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REACTIONS TO AN INFLUENZA VIRUS VACCINE IN INFANTS AND CHILDREN

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A RECENT report from this laboratory indicated that maximum antibody response in infants and children is not always achieved with a single injection of influenza virus vaccine.[1] In the course of that study reactions to the injected material were noted, and it seemed advisable to report, in some detail, the ill effects encountered.

It was readily apparent that the number of reactions was proportional to the amount of virus in the vaccine [2] and that the severity of the reactions was also related to the virus content. Furthermore, the frequency and severity appeared to be more pronounced than experience with adult groups had demonstrated. These observations, as well as some discussion of dosage of influenza virus vaccines, comprise the bulk of the report. The study was conducted with three groups of approximately 30 children each, whose average age was

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This study was conducted under the auspices of the Commission on Influenza, Army Epidemiological Board, Office of the Surgeon General, United States Army, Washington, D. C.

From the Virus Laboratory, Department of Epidemiology, School of Public Health, and the Department of Pediatrics and Communicable Diseases, University of Michigan Medical School.

1. Quilligan, J. J., Jr.; Minuse, E., and Francis, T., Jr.: Homologous and Heterologous Antibody Response of Infants and Children to Multiple Injections of a Single Strain of Influenza Virus, J. Clin. Investigation, **27**:572-579, 1948.

2. (*a*) Grant, H. B.: Influenza Virus Vaccine, J. Pediat. **29**:485-486, 1946. (*b*) Salk, J. E.: Reactions to Concentrated Influenza Virus Vaccines, J. Immunol. **58**:369-395, 1948. (*c*) Cohen, P., and Schneck, H.: Effect of Influenza Virus Vaccination in Infants and Children, with Antibody Studies, J. Pediat. **32**:161-169, 1948. (*d*) Dukes, R. E., and Gillespie, J. B.: Immunization of Children with Influenza Virus Vaccine, Illinois M. J. **93**:252-254, 1948.

3.2 years. The type A PR8 strain of influenza virus [3] was used, and multiple injections of small and large doses of vaccine were given, with various intervals of time between injections.

MATERIALS AND METHODS

Subjects.—The study was conducted at the Sarah Fisher Home, Farmington, Mich. Ninety-three children, whose average age was 3.2 years, were divided into three groups. No influenza virus vaccine had been given to any of these children nor had there been any infections with type A influenza virus in the institution in the preceding three year period. Any child with allergic tendencies was omitted from the study.

Vaccine.—The vaccine was obtained from the Lederle Laboratories, Pearl River, N. Y., through the courtesy of Dr. H. C. Cox, and was prepared in the following manner: Ten day old embryonated hens' eggs were inoculated with the PR8 strain of the type A influenza virus and the eggs then incubated for forty-eight hours,

Reactions Encountered in the Vaccination Program

	I. A Large Dose Every Other Week for 5 Weeks					II. A Small Dose Every Other Week for 5 Weeks					III. A Small Dose Every Other Day 5 Times				
Date of Administration	8-27	9-11	9-25	10-8	10-24	8-28	9-12	9-26	10-9	10-25	8-29	8-31	9-2	9-4	9
Amount of Vaccine *	1.0	0.65	0.65	0.65	0.65	0.13	0.13	0.13	0.13	0.13	0.13	0.13	0.08	0.13	0.1
Temperature elevation (100 F. and above)	23	1	2	1	2	1	1	..	1	2	6	5	..	1	
Temperature elevation persisting longer than 24 hours	7	..	..	..	..	..	..	..	..	..	..	..	..	..	
Prostration	11	1	..	..	..	..	..	..	..	..	5	3	..	..	
Nausea	9	..	1	..	..	..	..	..	..	..	3	2	..	..	
Vomiting	7	..	1	..	..	..	..	..	..	..	3	2	..	..	
Other	14	..	..	..	..	..	..	..	..	..	4	2	..	..	
Total number of children with any type of reaction (numerator) in group receiving vaccine (denominator)	24/31	1/27	2/30	1/28	2/30	1/30	1/28	0/26	1/26	2/25	7/32	5/32	0/24	1/31	1/

* Cubic centimeters of unconcentrated infected allantoic fluid.

at which time the allantoic fluid was harvested and then concentrated by centrifugation two times in a Sharples centrifuge. This resulted in a twentyfold concentrate of the infected allantoic fluid as originally harvested. The concentrated material had a protein content of 2 mg. per cubic centimeter and a chicken erythrocyte agglutination titer of 2,140 [4] by the method of Hirst and Pickels [5] and of 10,240 by a test tube pattern method.[6] The original material was diluted 1:2, 1:15 and 1:72. The respective titers for these dilutions, by use of the test tube pattern method, were 5,120, 640 and 128.

3. Francis, T., Jr.: Transmission of Influenza by Filterable Virus, Science **80**:457-459, 1934.

4. All titers are expressed as the reciprocal of final dilution of virus.

5. Hirst, G. K., and Pickels, E. G.: A Method for the Titration of Influenza Hemagglutinins and Influenza Antibodies with the Aid of a Photoelectric Densitometer, J. Immunol. **45**:273-283, 1942.

6. Salk, J. E.: A Simplified Procedure for Titrating Hemagglutinating Capacity of Influenza Virus and the Corresponding Antibody, J. Immunol. **49**:87-98, 1944.

It should be pointed out that this vaccine preparation contained only one strain of virus, whereas the commercially available vaccines contain two or more strains of virus.

Administration of Vaccine.—The dates of administration and the amounts of vaccine given are listed in the table. The latter are expressed in terms of the equivalents of unconcentrated infected allantoic fluid. However, the first dose for group I was 0.1 cc. of a 1.2 dilution of the original twentyfold concentrated material and subsequent doses in this group were 0.5 cc. of the 1:15 dilution of the concentrated preparation. The doses for groups II and III were 0.5 cc. of the 1:72 dilution of the twentyfold concentrate.

The table shows that the children were divided into three groups of approximately 30 children each and that not all of them received every dose of vaccine. In group I the amount of vaccine was reduced because of the large number of reactions that developed. In group III the dose was decreased for the third injection and the number reduced by those children who had had reactions with the first or second dose. However, the latter children were given the last two doses. Those other instances in which vaccine was not given were unavoidable because of absence from the institution or other reasons.

The vaccine was given subcutaneously and usually in a volume of 0.5 cc. Before each inoculation, 0.02 cc. of the 1:72 dilution was given intradermally on the flexor surface of the left forearm. The site of inoculation was then observed for thirty minutes. If minimal erythema was present, 0.1 cc. was given subcutaneously and the child observed for an additional thirty minute period. No further untoward effects were ever noted. The remaining 0.4 cc. in the dose was given subcutaneously.

Observation of Subjects.—Rectal temperatures were recorded for all children on the day before an injection, on the morning an injection was to be received and, finally, on the morning following an injection. If at any time after receipt of a dose of vaccine any unusual actions were noted, then the course of the temperature was followed at four hour intervals. In several of the younger subjects, the obvious difficulty of interpretation of subjective symptoms arose. Most of the observations were made by the cottage attendants, all of whom were thoroughly familiar with the children and most of whom were registered nurses.

RESULTS

The reactions that occurred in the three groups are summarized in the table. The general statement may be reemphasized that reactions are largely a function of the amount of virus in the preparation. The greatest number of reactions occurred in group I to which the largest amount of vaccine was given. Approximately four to six hours after the first dose of vaccine, several children were noted to have refused supper or vomited without warning. In this group, in which the ill effects were most severe, elevations in temperature up to 105 F. were recorded, as well as extreme prostration and, in 2 children, twitchings of the extremities. Most frequently, the only evidence of reaction was an elevation of temperature. Approximately one third of the children reacting to the first dose in group I had fever that continued for more than twenty-four hours, an effect approaching the natural form of

the disease. The other less severe reactions tended to manifest themselves after the few severe ones had subsided. The amount of virus in subsequent doses in this group was reduced and the number of reacting children decidedly decreased. Seemingly, the first dose used (0.1 cc. of the 1:2 dilution of twenty times concentrated infected allantoic fluid) was the maximum which could be tolerated by children of this age. Further injections of vaccine in group I consisted of 0.5 cc. of the 1:15 dilution of vaccine (0.65 cc. of unconcentrated infected allantoic fluid), and the number of reactions diminished and was comparable to that observed in the other two groups of children.

Group III had the second largest number of reacting children. Eight children who reacted after the first and/or second dose of vaccine did not receive the third dose of vaccine, and the amount of virus given in the third dose was decreased. However, all but 1 child received the fourth and fifth doses, with only one instance of ill effect on either occasion. The similarity of these observations to results with bacterial pyrogens in rabbits, in which an increasing tolerance to repeated daily injections was found, should be pointed out.[7]

Group II experienced the least number of reactions. It is difficult to understand the reason that the number of children in group III with reactions to the first dose should be so much greater than the number in group II, to which the same amount of vaccine was given. Perhaps with greater numbers of children such differences would not be apparent, and the results of the first small dose of vaccine might be more suitably expressed as the occurrence of reactions in 8 children of a total of 62. However, any further coupling of the data in groups II and III would be invalid because of the differences in the intervals of time between inoculations of the vaccine. The difference in reactions in the later instances might well be related to the interval of time between injections and to the fact that in group II antibody to the reactive material or the virus material is developed sufficiently in the two week interval between injections and acts to neutralize further injections of antigen.[8] Along this line it has been shown that persons who react after a single injection of vaccine will react again when reinoculated six months after the first dose.[2b] If a resistant period does occur, it seems reasonable to assume that the interval of time between injections is an important element in the process.

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7. Beeson, P. B.: Tolerance to Bacterial Pyrogens: I. Factors Influencing Its Development, J. Exper. Med. **86**:29-38, 1947.

8. Beveridge, W. I. B.; Stone, J. D., and Lind, P. E.: Suppression of Antigenicity of Influenza Virus by Admixture with Homologous Antiserum, Australian J. Exper. Biol. & M. Sc. **22**:307-309, 1944.

The possibility was entertained that the volume of fluid injected might influence the rapidity of absorption of vaccine and result in increased reactions when the smaller volumes were used. An attempt to answer this question was made in the following way: Two groups of 25 children were selected. One group was given injections of 0.1 cc. of vaccine, the other 1 cc., both doses containing the same amount of inactivated virus. Reactions in the two groups were the same, indicating that, within the amounts used, the volume of fluid was not a significant factor.

Although the evidence for systemic reactions was usually clearcut, there was surprisingly little indication of local reaction. At the site of subcutaneous inoculation, some children had swelling and redness, with associated heat and pain. However, such observations were less frequent than we anticipated.

Skin testing in the three groups yielded no significant results. Slight erythema fifteen to twenty minutes after an intracutaneous injection was occasionally noted. No pronounced effects of a sensitizing type were seen, although a few children were given a divided dose of vaccine because of doubtfully positive cutaneous reactions after thirty minutes. The absence of allergic reactions probably depended on the elimination from the study group of any children with allergic backgrounds. However, definite reactions of an allergic type have been reported when vaccines made from egg-grown virus were given to persons with known allergy to eggs.[9]

COMMENT

In this study, the use of 0.1 cc. of the 1:2 dilution of twenty times concentrated infected allantoic fluid (equivalent to 1 cc. of unconcentrated infected allantoic fluid) resulted in reactions that clearly represented the maximum in terms of severity and number of children involved (table). On the other hand, with the use of only the equivalent of 0.13 cc. of unconcentrated infected allantoic fluid, the reactions encountered were mild and, by the use of multiple injections, the mean antibody response to the homologous virus strain was adequate.[10] It, therefore, seems reasonable to postulate the use of an amount of inactive virus intermediate between that given to the children in group I and that given those in the other two groups. In terms of unconcentrated infected allantoic fluid, this means that somewhere between

9. Ratner, B., and Untracht, S.: Allergy to Virus and Rickettsial Vaccines: I. Allergy to Influenza A and B Vaccine in Children, J. A. M. A. **132**:899-905 (Dec. 14) 1946.

10. Francis, T., Jr.: Quantitative Relationships Between the Immunizing Dose of Epidemic Influenza Virus and the Resultant Immunity, J. Exper. Med. **69**:283-300, 1939.

0.65 and 0.13 cc. represented the proper amount of virus for an adequate stimulus, resulting in increased resistance of the individual person. This amount of vaccine, given to young children who have had little or no experience with the influenza viruses, should be repeated at least two times and probably three times for three reasons: (1) to minimize the harmful effect of too large a dose, (2) to increase the experience span of the child's immune mechanism to the stimulus of influenza virus antigens and (3) to achieve a better antibody response.

It should be reemphasized that the preparation used in this study was concentrated and contained only a single strain of influenza virus. The commercial preparations usually have three strains of virus and the response to them will not be entirely the same. All commercial preparations are concentrated in some manner, such as centrifugation,[11] adsorption-elution [12] or by adsorption onto calcium phosphate.[13] If it is possible to know the concentration of the infected egg fluid, a rational means for arriving at the proper dosage is available. It should be further shown that the biologic characteristics of the vaccine are adequate in order to insure uniform products.[14] Other reports in the literature have demonstrated the excessively harmful effects that may occur after large doses of influenza virus vaccine are given to infants and young children.[15] Although some authors expressed their belief that the ill effects they observed were due to factors other than the virus content, it is important to remember that the bulk of reactions encountered with influenza vaccines are due to the virus content and not to the nonspecific effect of the egg protein. When persons to be vaccinated are properly selected, the reactions to the egg protein are rare. Certainly, persons with known egg sensitivity should not receive the vaccine, and in young infants, if egg has not been a common food, skin tests should be carried out before vaccine is administered.

The number of doses of vaccine should receive some further consideration. It will be noted that continued injections of vaccine, even when given every other day, did not result in excessive reactions nor were there any untoward evidences of sensitization when the vaccine was given every other week for 5 doses. Then apparently, from these

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11. Stanley, W.: An Evaluation of Methods for the Concentration and Purification of Influenza Virus, J. Exper. Med. **79**:255-266, 1944.

12. Francis, T., Jr., and Salk, J. E.: A Simplified Procedure for the Concentration and Purification of Influenza Virus, Science **96**:499-500, 1942.

13. Salk, J. E.: Partial Purification of the Virus of Influenza by Adsorption on Calcium Phosphate, Proc. Soc. Exper. Biol. & Med. **46**:709-712, 1941.

14. Francis, T., Jr.: The Development of the 1943 Vaccination Study of the Commission on Influenza, Am. J. Hyg. **42**:1-11, 1945.

15. Lapin, J. H.: Prophylaxis of Upper Respiratory Infections in Children by Oral Penicillin and Influenza Virus Vaccine Inoculation, Arch. Pediat. **64**:121-131, 1947. Footnote 2.

observations, multiple injections in a selected group of children were not harmful. The mean titers of antibody response reported elsewhere [1] were greatest after the third dose of vaccine in the younger children of the two groups that received the vaccine every other week. The fourth and fifth doses were not contributory to the height of antibody response and some fall in the mean titers of the three groups occurred five months after vaccination, although the antibody titers against the homologous strain of virus were still at protective levels.[1]

CONCLUSIONS

With proper dosage and intervals between doses, few reactions to an influenza virus vaccine resulted in groups of children whose average age was 3.2 years.

The reactions to influenza virus vaccine administered to infants and children are due, in most instances to the amount of virus in the vaccine. Such reactions can be minimized by the use of multiple injections of small amounts of vaccine with short intervals between injections.

Despite the use of multiple doses of vaccine, given in one instance every other day five times and in two other instances every other week five times, no evidence of sensitization in any of the selected children who received the vaccine was observed.

Sister Remie and Sister Eugenie, from the House of Providence, and Dr. S. Van Schooten, of Detroit, assisted in this study.

PSEUDOREACTIONS TO THE TUBERCULIN PATCH TEST

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PSEUDOREACTIONS to tuberculin may cause undue anxiety, unwarranted treatment and expense and psychologic harm. The nature, frequency and characteristics of such pseudoreactions to the Mantoux test have been discussed in a previous publication.[1]

Pseudoreactions to the tuberculin patch test are a rarity. None were encountered during the experimental period in which old tuberculin from the New York Department of Health was used. They occurred occasionally when the concentration of tuberculin was increased to four times that of standard old tuberculin. For a short period during the war, their frequency increased so conspicuously that an investigation of their origin became imperative. A long search into all eventualities finally revealed the probable cause. A few batches of tuberculin had been concentrated at temperatures between 50 and 60 C. (122 to 140 F.) instead of at 100 C. (212 F.). Resumption of the conventional method of tuberculin concentration, at 100 C., made pseudoreactions to the tuberculin patch test almost disappear. The significance of this observation will be discussed later.

As can be seen, the frequency of pseudoreactions has varied, and no exact percentage figures can be given. It must be well below 1 per cent, since I have seen but 11 cases during a period of ten years in which many thousands of tests have been made. In spite of their rarity, attention is called to their occurrence in order that diagnostic errors and their consequences may be avoided.

TYPES OF PSEUDOREACTIONS

Pseudoreactions to the tuberculin patch test, in a strict sense, are set apart from other cutaneous manifestations which may follow the application of the test:

1. Brownish discoloration in square form corresponding with the tuberculin patches, and seen when the test is removed, results from staining of the skin surface with tuberculin. The brown spots can easily be washed off, leaving normal skin; they do not resemble any cutaneous reaction.

1. Vollmer, H., and Ripps, M. L.: Pseudoreactions to Tuberculin, Am. J. Dis. Child. **65**:763 (May) 1943.

2. Persons hypersensitive to adhesives may show a cutaneous reaction which is a "negative" of a true or false reaction to the patch test. Erythema appears in the whole area of skin which was in contact with the adhesive tape, while the areas covered by the patches stand out as three squares of normal skin. These unspecific reactions to adhesives usually fade rapidly after the removal of the test and cannot easily be confused with positive reactions to the patch test.

3. Persons with excessive perspiration show occasionally a faint miliarial rash at the area covered by the patch test; it may be accentuated underneath the filter paper patches where more moisture seems to accumulate. This is an inflammation around the sweat glands caused by perspiration. It is not indurated and is less elevated and fainter than a true reaction to tuberculin. This reaction decreases rather than increases in intensity after removal of the patch test. Attention to these points may prevent misinterpretation.

4. Sensitivity to the culture medium, if it exists, might manifest itself as three equal cutaneous reactions, in square form, to the control, as well as to the tuberculin, patches. This seems to be rare; only 1 case has been encountered throughout the years.

DIFFERENCES FROM TRUE POSITIVE REACTIONS

In contrast to these phenomena, pseudoreactions to the tuberculin patch test, as here understood, have the same distribution in the area of the patch test as have true positive reactions. They are unspecific skin reactions confined to the areas covered by the two tuberculin patches. They differ from true positive reactions in certain characteristics:

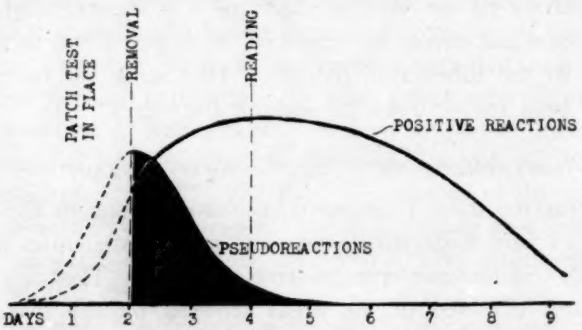
1. They occur almost exclusively in persons with a personal or family history of allergy.

2. They appear and fade more rapidly than true positive reactions. Pseudoreactions have reached their maximum intensity at the time the patch test is removed; thereafter they subside rapidly, most of them disappearing within two to three days. In contrast, true positive reactions usually increase in their intensity after removal of the test. Some reactions develop only after removal of the patch test; the majority reach their maximum intensity forty-eight hours after removal of the test, some even later. Almost all positive reactions are still visible after one week, when the majority of pseudoreactions have completely disappeared. The figure shows schematically the different courses of true positive reactions and pseudoreactions. It illustrates that a second reading of the test after one week should permit correct interpretation.

3. The clinical appearance of pseudoreactions also differs from that of true reactions. Pseudoreactions consist essentially of erythema with or without a slight degree of swelling, occasionally intensified at the follicles. They present the clinical picture of an irritative dermatitis, localized in the epidermal layer of the skin. True positive reactions involve deeper layers of the skin and consist of lichenoid-follicular eruptions and, not infrequently, vesiculation, with induration.

CAUSE OF PSEUDOREACTIONS

What is the cause of pseudoreactions to the tuberculin patch test? They cannot be due to sensitivity to the culture medium, since they do not develop underneath the control patch of the test. Like pseudoreactions to the Mantoux test, they must be ascribed to the tuberculin itself which, in some persons, seems to act as a primary cutaneous irritant causing dermatitis. Whether tuberculoprotein itself or an



Graph showing course of pseudoreactions and of true positive reactions to the tuberculin patch test.

impurity is responsible cannot be decided. Apparently, the offending substance is destroyed or its irritative quality reduced by prolonged heating at 100 C. This is at least the most acceptable explanation for the higher incidence of pseudoreactions observed when lower temperatures (50 to 60 C.) were used for the concentration of tuberculin. Pseudoreactions practically disappeared when heating at a temperature of 100 C. was resumed. It is known that diphtheria toxin, too, may cause pseudoreactions and that heating at 75 C. (167 F.) leaves almost unaltered the proteinic substances causing pseudoreactions.

The rarity of pseudoreactions to the tuberculin patch test as compared with the intracutaneous test may be explained by the relatively small amount of tuberculin absorbed by the skin. The incidence of pseudoreactions seems to be a function of the concentration of the offending substance, as well as of the degree of individual skin sensitivity.

To identify a pseudoreaction to the tuberculin patch test, a subsequent intracutaneous test suggests itself. However, it is of little help unless the Mantoux reaction is negative. Persons with a pseudoreaction to the patch test also frequently show a pseudoreaction to the intracutaneous test. Although different layers of skin play a part in pseudoreactions to the two tests, both skin layers of the same person may be equally sensitive to the offending substance.

It might be doubted that the reactions here described are pseudoreactions rather than weak positive reactions. The 11 children with this form of reaction were thoroughly investigated and failed to show any evidence of a tuberculous infection. Six of them had, at a later date, negative reactions to the patch test or to the intracutaneous tuberculin test. In the remaining 5, definite proof was lacking. However, in all 11 children the reactions were distinctly different from true reactions, and, if they were weak positive reactions, their rarity would not be understandable.

SUMMARY

Pseudoreactions to the tuberculin patch test are rare. Their frequency increased temporarily when temperatures between 50 and 60 C., instead of 100 C., were used for the concentration of tuberculin.

These pseudoreactions are ascribed to a constituent of tuberculoprotein which acts as a primary cutaneous irritant, causing dermatitis. The irritative quality of the offending substance seems to be decreased by prolonged heating at a temperature of 100 C.

Pseudoreactions to the tuberculin patch test occur mainly in persons who are allergic or who have a family history of allergy. They differ from true positive reactions in that they appear and fade more rapidly; they consist essentially of erythema with or without a slight swelling, and they lack the lichenoid-follicular and vesicular form elements, as well as the induration, of positive reactions. A second reading four to seven days after removal of the patch test may prevent errors; by this time pseudoreactions have faded, while true reactions are still visible.

25 Central Park West.

CHOREA (SYDENHAM)

A Study of Fifty-Eight Additional Patients

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IN A STUDY of 107 patients with chorea (Sydenham), one of us (B. M. K.) and Mirman [1] observed that chorea with an increased erythrocyte sedimentation rate was in most instances associated with active rheumatic fever. Patients who (in the absence of cardiac failure) had a normal erythrocyte sedimentation rate during the early part of their chorea had no symptoms or signs of rheumatic disease at that time or at any time during a long follow-up period. In that study 15 such patients were followed for five to fifteen years and 14 were followed for one to five years (29 patients for an average of five years), and none of these showed any evidence of rheumatic disease at any time. A review of the literature was included in that study.

In this report, the results of a study of 58 additional patients with chorea are presented. This study is significantly different from the previous one in that the patients were admitted to Herrick House from the various children's hospitals in the city of Chicago. Patients admitted from Michael Reese Hospital were excluded.[2]

The purpose of this study was to determine whether data collected from various sources under relatively less uniform conditions would

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From the Kunstadter Laboratories for Pediatric Research, the Medical Research Institute of Michael Reese Hospital, the Herrick House for Rheumatic Fever and the Department of Pediatrics, University of Illinois College of Medicine.

1. Kagan, B. M., and Mirman, B.: Sydenham's Chorea: A Syndrome for Differential Diagnosis, J. Pediat. **31**:322-332 (Sept.) 1947.

2. Permission to use data on these patients obtained during episodes of chorea either prior to or following their stay at Herrick House was given by the Pediatric Department, Cook County Hospital, the Children's Memorial Hospital and the Pediatric Department of the Research and Educational Hospitals, University of Illinois. Patients who were admitted to Herrick House from Michael Reese Hospital or who were at any time admitted to Michael Reese Hospital were not included in this study because they had already been included in the previous one.[1]

yield results similar to those obtained in the previous study in which the data were collected at one individual hospital (Michael Reese Hospital). At the various hospitals electrocardiograms, erythrocyte sedimentation rates and roentgenologic examinations were performed in different ways and interpreted along slightly different lines. There is ground, therefore, for inquiring as to the effect the various interpretations given at the different hospitals might have on the results obtained.[2] If, in spite of the inevitable decrease in uniformity of results obtained in a study based on such different methods and interpretations, the basic principles suggested by the previous study were confirmed, considerable weight would be added to their soundness. An unfortunate but major difference between this study and the previous one is that (on these patients) a long term follow-up period was not practical. The data, therefore, pertain primarily to active episodes of chorea and to the subsequent period of convalescence at Herrick House.

Erythrocyte sedimentation rates were determined by various methods in the different hospitals from which patients came. These included the Wintrobe and Landsberg,[3] the Cutler,[4] the Landau [5] and the original Linzenmeier methods.[6] We refer to the results as normal or increased in accordance with the interpretation given these tests in the various hospitals concerned. Only erythrocyte sedimentation rates done within three weeks after the onset of chorea were considered in the analysis. In this series, the date of onset of chorea was accepted to be that estimated by the physician who wrote the history of each patient. It is subject, therefore, not only to the usual difficulty in determining the exact time of onset of this malady but also to different interpretations of histories by the various examining physicians.

DEFINITIONS

Such manifestations as the following were considered as supporting evidence of rheumatic fever: arthralgia, arthritis, subcutaneous nodules, active rheumatic carditis, erythema multiforme, erythema marginatum, erythema nodosum, fever unascribed to other causes and epistaxis. Of course, one, or perhaps more, of these symptoms or signs occurring in a patient may be due to causes other than rheumatic fever. Neverthe-

3. Wintrobe, M. M., and Landsberg, J. W.: A Standard Technique for the Blood Sedimentation Test, Am. J. M. Sc. **189**:102-114 (Jan.) 1935.

4. Cutler, J.: Graphic Methods for the Blood Sedimentation Test, Am. Rev. Tuberc. **19**:544-558 (May) 1929.

5. Landau, A.: Microsedimentation (Linzenmeier-Raunert Method): Its Serviceability and Significance in Pediatrics; Use of Modified Apparatus with Simplified Technic, Am. J. Dis. Child. **45**:691-734 (April) 1933.

6. Linzenmeier, G.: Untersuchungen über die Senkungsgeschwindigkeit der roten Blutkörperchen, Arch. f. d. ges. Physiol. **181**:169-183 (June) 1920.

less, for the purposes of this study, they were considered to be rheumatic whenever a clinical diagnosis of rheumatic fever had been made by the referring agency. Active rheumatic heart disease was considered to be present when there was evidence of progressing cardiac involvement, such as changing murmurs, presence of a friction rub, a palpable thrill or a gallop rhythm, change in the contour of the heart seen on the roentgenogram or significant change in the electrocardiogram. Inactive rheumatic heart disease was considered to be present when there was evidence of heart disease and a history of previous rheumatic carditis but no evidence of change in the heart on repeated clinical examination, no change in cardiac contour on repeated roentgenograms and no significant change in serial electrocardiograms.

DATA

The patients were grouped in the following manner:

Group I: Patients on whom pertinent data obtained during initial episodes of chorea were available.

a. Patients with an increased erythrocyte sedimentation rate.

b. Patients with a normal erythrocyte sedimentation rate.

Group II: Subsequent episodes of chorea among patients of group I.

a. Patients from group I *a.*

b. Patients from group I *b.*

Group III: Patients on whom significant data about the first episode of chorea were not available but about whose subsequent episode, or episodes, pertinent information was obtained.

a. Patients with a history of a previous episode of rheumatic fever.

b. Patients without evidence of rheumatic fever in the history.

There were 50 patients (group I) on whom pertinent data were available during their initial episodes of chorea, and there were 8 patients (group III) on whom significant data during their first episode were not available.

Group I a. Initial Episodes of Chorea with Increased Sedimentation Rates.—Of the 50 patients on whose initial episodes of chorea data were available, 32 had increased erythrocyte sedimentation rates. Twenty-three of these had other evidences of active rheumatic fever at the time, and of these, 19 had active rheumatic heart disease at that time.

Eight patients of this group of 32 had chorea and an increased erythrocyte sedimentation rate but no other evidence of rheumatic activity or of heart disease at any time. Recurrences in this particular group were especially interesting. They are described under group II *a*, later.

In one other patient in whom the erythrocyte sedimentation rate was increased, no other evidence of rheumatic activity at that time was present. However, this patient had had two previous episodes of acute rheumatic fever without chorea. During the first episode of rheumatic fever this patient had a "loud blowing systolic murmur" at the apex, and the clinical diagnosis of rheumatic carditis was made. No change in either the electrocardiogram or the roentgenogram was apparent at that time. During the second episode of acute rheumatic fever and during the third, when the patient had chorea for the first time, there was no change in the cardiac status either clinically or on electrocardiogram or roentgenogram. The clinical impression was that the heart disease was inactive during both the second episode of rheumatic fever and the third episode, when the patient had chorea.

Group I b. Initial Episodes of Chorea with Normal Erythrocyte Sedimentation Rates.—Of the 50 patients on whom data are available during the original episode, 18 had a normal erythrocyte sedimentation rate. Not one of these patients showed any other evidence of rheumatic fever during these admissions. In a previous study [1] we reported on 50 other patients who had chorea with a normal erythrocyte sedimentation rate, and none of these had other evidence of rheumatic fever either at the time of the choreic episode or at any time during a long follow-up period. Twenty-nine of the latter patients were followed for an average of five years after the initial episode of chorea, and during this entire time none of them showed any evidence of rheumatic fever.

Group II. Subsequent Episodes of Chorea in Patients of Group I.—Group II *a*: Patients from group I *a*. Of the 32 patients who had increased erythrocyte sedimentation rates during their original episodes of chorea, 6 had one recurrence and 1 had two recurrences, a total of eight recurrences. One patient had a recurrence which was similar in all respects to his first episode. His erythrocyte sedimentation rate was increased; there were other signs of active rheumatic fever and evidence of active rheumatic carditis. Another patient had a recurrence of chorea two days after returning home from the hospital. At this time she had a normal erythrocyte sedimentation rate, no other evidence of rheumatic activity and inactive rheumatic heart disease. One patient had a recurrence which was similar to his original episode in that in both instances cardiac involvement was not evident, the erythrocyte sedimentation rate was increased and there were other evidences of rheumatic activity.

Of particular interest are the five recurrences among the 8 patients whose initial episodes were characterized by an increased erythrocyte sedimentation rate with no other evidence of rheumatic activity or cardiac involvement. Three patients had exactly similar recurrences, and 1 of these had a second recurrence with a normal erythrocyte

sedimentation rate and no other evidence of rheumatic activity or of cardiac involvement. One had a first recurrence with a normal erythrocyte sedimentation rate, no other evidence of rheumatic activity and no evidence of heart disease. These 8 patients, in their original episodes and in their total of five recurrences, showed no evidence of rheumatic disease or of cardiac involvement at any time. Two of the recurrences were associated with normal erythrocyte sedimentation rates. It is to be noted that in all but three of the original episodes in these patients the erythrocyte sedimentation rates were only a few millimeters above the accepted normal for the method used. It appears, therefore, that the conditions in some of these patients may be similar to those of group I *b*, the only difference being a slightly elevated erythrocyte sedimentation rate in these children. The slightly elevated erythrocyte sedimentation rate in these patients may have been due, of course, to many causes other than rheumatic fever.

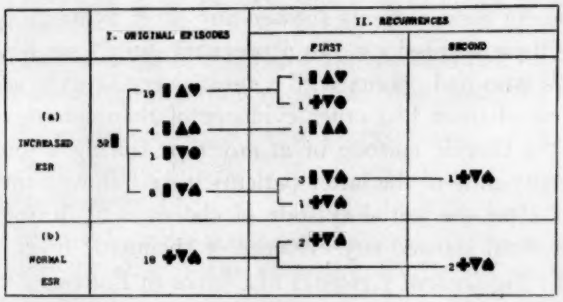

Fig. 1.—Summary of data obtained on patients studied during original episodes of chorea and their recurrences (groups I and II). The bar indicates increased erythrocyte sedimentation rate (*ESR*); the cross, normal erythrocyte sedimentation rate; the triangle, presence of other rheumatic manifestations; the inverted triangle, absence of other rheumatic manifestations; the heart, presence of active heart disease; the inverted heart, absence of heart disease, and the circle, presence of inactive heart disease.

Group II *b*: Patients from group I *b*. Of the 18 patients who had normal erythrocyte sedimentation rates during their original episodes and no evidence of rheumatic activity or cardiac involvement, 4 had recurrences. Two of these 4 patients had one recurrence each, during which the erythrocyte sedimentation rate was again normal and there was no evidence of either cardiac involvement or rheumatic disease. The other 2 patients had two recurrences each. At the time of the first recurrences in the latter patients, the erythrocyte sedimentation rates were not obtained, but the records revealed neither clinical nor other laboratory evidence of rheumatic activity or cardiac involvement at that time. These first recurrences are not shown in figure 1 because the erythrocyte sedimentation rates were not available. Moreover, the

second recurrences in these 2 patients again revealed normal erythrocyte sedimentation rates with no evidence of rheumatic activity or cardiac involvement. Thus, in this significant group the recurrences, as well as the original episodes, were accompanied with no evidence of rheumatic disease in association with the chorea.

Group III. Subsequent Episodes of Chorea in Patients on Whom Significant Data Were Not Available During the Initial Episode.—There were no data available on the initial choreic episodes of 8 of the 58 patients with chorea. Seven of these patients gave a history of a previous episode of rheumatic fever and they are considered in group III *a*. The other patient, although she had been seen during the initial episode, had had no erythrocyte sedimentation rate recorded at that time. Since there was no evidence of rheumatic fever during the initial episode or at any time in the history, this patient is considered in group III *b*.

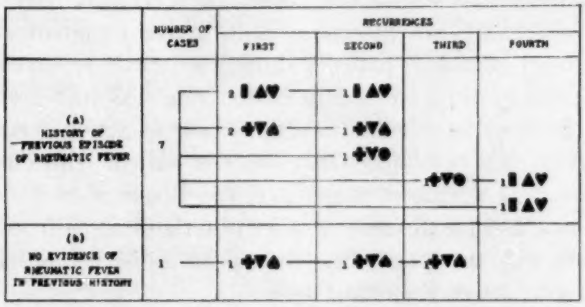

Fig. 2.—Summary of data obtained on patients not seen during original episode of chorea but seen during recurrences (group III). See legend to figure 1 for key to symbols.

Group III *a*: Patients with a history of a previous episode of rheumatic fever. Of these 7 patients 4 were seen during a first recurrence and 2 of these 4 during a second recurrence as well; 1 was seen during the second recurrence only, 1 during the third and fourth recurrences only and 1 during only the fourth recurrence. Thus, a total of ten recurrences was studied in these 7 patients.

An individual analysis of these 7 patients reveals that during their first recurrence 2 had increased erythrocyte sedimentation rates and other evidence of rheumatic activity and rheumatic heart disease. One of these had a second recurrence, again with an increased erythrocyte sedimentation rate and similar evidence of rheumatic disease. These, therefore, corresponded to the patients who had chorea associated with rheumatic fever, such as were studied in group I *a*. Two of the 7 patients had a first recurrence with a normal erythrocyte sedimentation rate and no other evidence of rheumatic activity or heart disease, and 1 of these 2 patients had a similar second recurrence. For these

2 patients, we have only a history of previous rheumatic fever. It is not clear, therefore, whether their conditions were chorea associated with rheumatic fever or not. One of the 7 patients was seen for the first time during a second recurrence, at which time she had a normal erythrocyte sedimentation rate, no other evidence of rheumatic activity and evidence of inactive heart disease.

Another of this group of 7 was seen first during a third recurrence with a normal erythrocyte sedimentation rate, no other evidence of rheumatic activity and inactive heart disease. This patient was seen also during a fourth recurrence with an increased erythrocyte sedimentation rate, other evidence of rheumatic activity and evidence also of active rheumatic heart disease. These 2 patients obviously had had rheumatic fever. They were also seen during an episode of chorea when the erythrocyte sedimentation rate was normal with no other evidence of rheumatic activity. This suggests that perhaps patients who have once had chorea associated with active rheumatic fever may have recurrences of chorea which are not associated with active rheumatic fever. We have data on 1 of the 7 patients during a fourth recurrence only, at which time the erythrocyte sedimentation rate was increased and there was other evidence of rheumatic activity and of active rheumatic heart disease. It is clear, therefore, that, when a patient with chorea is seen for the first time during a recurrence, the presence of a normal sedimentation rate and the absence of other criteria of active rheumatic fever do not rule out the possibility that prior episodes of chorea were associated with active rheumatic fever.

Group III *b*: Patients without evidence of rheumatic fever in previous history. There is 1 patient in this group. The patient was seen during the initial episode of chorea but could not be considered in group I because a determination of the erythrocyte sedimentation rate was not done at that time. There were no symptoms or signs of rheumatic disease during that initial episode. This patient was seen during the first, second and third recurrences, during each of which the erythrocyte sedimentation rate was normal and there were no evidences of rheumatic disease or of heart disease. This patient's chorea was at times maniacal. The first episode followed the death of a maternal grandmother to whom the patient was extremely attached. Her mother worked at night as a waitress and her father had been absent from home for two years. Unfortunately, more information about possible dynamics of this case is not available. There was no evidence of rheumatic disease at any time.

CONCLUSION

This study is significant because the data were obtained from four institutions using various methods for obtaining electrocardiograms, roentgenograms and erythrocyte sedimentation rates, as well as different

clinical approaches for the study of rheumatic fever and heart disease. In spite of the different sources and methods, the data so obtained proved to be essentially similar to those reported from the Michael Reese Hospital in a previous study.[1] These observations lend further support to the concept that in not all patients with chorea (Sydenham) is the condition associated with rheumatic fever and that, specifically, an initial episode of such chorea in a person with a normal erythrocyte sedimentation rate and no other evidence of rheumatic fever is probably not due to rheumatic fever. As a result of these studies, it is recommended that such conditions be referred to as "chorea (Sydenham), cause undetermined" in order to avoid any implication that they are due to rheumatic fever with all its possible sequelae. The data indicate that chorea seen during a first episode with an increased erythrocyte sedimentation rate is most likely associated with rheumatic fever. In the absence of other rheumatic manifestations, however, it is difficult to establish with certainty that these patients have rheumatic fever. In other words, a diagnosis of "chorea (Sydenham), associated with rheumatic fever" should be made with certainty only when there is other evidence on which a diagnosis of rheumatic fever can be made.

Patients who have chorea associated with rheumatic fever may have similar recurrences or may have recurrences during which there are no other evidences of rheumatic fever. Patients who have chorea which is not associated with rheumatic fever ("chorea [Sydenham], cause undetermined") may be expected to have recurrences which are also not associated with rheumatic fever, and as a group they may be expected to experience no greater incidence of rheumatic fever or its sequelae than does the general child population.

Twenty-Ninth Street and Ellis Avenue (16).

SCARLET FEVER

Diagnostic Value of the Dick Test, White Blood Cell Counts, Throat Cultures and Desquamation

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AND
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THE USUAL case of scarlet fever presents little difficulty in diagnosis by clinical means. However, there remains an appreciable number of cases in which the picture is not typical and in which diagnostic aids are desired. It is these questionable conditions that frequently go unrecognized and patients with them spread the disease to many other susceptible persons.

The reversal of the Dick reaction from positive to negative in a series of tests performed during the course of the disease is frequently employed to confirm the diagnosis of scarlet fever. If valid, this procedure should be of particular importance to the clinician and epidemiologist. The value of the Dick test for measurement of susceptibility to scarlet fever is universally recognized; however, much doubt still remains with respect to the worth of this test in the diagnosis of scarlet fever.

The present investigation is a study of the reactions to the Dick test of patients with scarlet fever through various stages of the disease. During the course of this observation, total and differential white blood cell counts, results of cultures of material from the throat for hemolytic streptococci and the development of characteristic desquamation were carefully recorded to determine their value as aids in the diagnosis of this disease. The cases were classified as mild, moderate or severe, depending on the intensity of the rash.

METHOD

One hundred patients with scarlet fever were studied during November and December 1947. The patients had clearcut, unquestionable clinical evidence of scarlet fever and ranged from 2 years to 33 years of age, 94 per cent being

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* From the Philadelphia Hospital for Contagious Diseases.

Material for the Dick test was supplied by The National Drug Co., Philadelphia 44.

below 10 years of age. The series included persons with scarlet fever of various degrees of severity. The intensity of the rash was mild in 34 per cent of the patients, moderate in 45 per cent and severe in 21 per cent. For obvious reasons, it was necessary to choose only those who were in the early stages of the disease, the series being limited to patients who were seen less than two days after the onset of the rash. Patients who had previously been immunized against scarlet fever, or who were treated with antitoxin, were also excluded from this group but were considered separately, since the influence of these factors on the Dick reaction was not known.

A series of Dick tests was done, the first on the patient's admission to the hospital while he was in the receiving ward and the subsequent tests at ten day intervals, each patient receiving at least 3 tests. On admission, a culture of material from the throat was taken on a blood agar plate. A second throat culture was taken the following day, so that each patient had 2 throat cultures to be examined for hemolytic streptococci. Total leukocyte and differential blood cell counts were also made on the first day in the hospital.

TABLE 1.—*Reactions to Dick Test at Ten Day Intervals in One Hundred Patients with Scarlet Fever*

On Admission	On 10th Day of Disease	On 20th Day of Disease	Number of Patients
Positive	Positive	Positive	31
Positive	Positive	Negative	7
Positive	Negative	Negative	20
Negative	Negative	Negative	27
Negative	Negative	Positive	3
Negative	Positive	Positive	5
Negative	Positive	Negative	6
Positive	Negative	Positive	1
			100

To minimize variations in the reactions because of technic of administration, two intradermal injections of the scarlet fever streptococcus toxin U.S.P. were given. One-tenth cubic centimeter of the commercial product was injected intradermally on the volar surface of each forearm. All the toxin used was of fresh stock, prepared according to the specifications of the United States Public Health Service and obtained from the same commercial laboratory. The material for injection was standardized so that each cubic centimeter contained 10 skin test doses of the toxin.

Dick reactions were read eighteen to twenty-four hours after the injection and were recorded as positive when an erythema appeared measuring 10 mm. or more in diameter.

During convalescence, each patient was observed closely for the presence or absence of desquamation.

RESULTS

Of the 100 patients with scarlet fever who were studied, 59 had a positive reaction and 41 reacted negatively when given the Dick test soon after the onset of the rash. There was no appreciable difference in reaction between patients tested on the first and those tested on the second day of the exanthem.

Of the 59 patients who reacted positively to the initial Dick test, the reactions of 27 (45.7 per cent) became negative subsequently. This change is regarded as a reversal of the Dick reaction. Twenty, or 74 per cent, of the 27 patients who showed a reversal of the Dick reaction did so within the first ten days.

In 14 patients, the Dick reaction became positive ten days after the initial negative reaction to the test.

Of another group of 15 patients who received scarlet fever streptococcus antitoxin U.S.P. therapeutically, the initial Dick reaction was negative in 14. There was 1 patient in this group whose reaction was positive throughout the entire period of observation. Four patients who had a negative reaction on the initial Dick test, and on the second test ten days later, showed a positive reaction on the twentieth day.

TABLE 2.—*Distribution of Patients with Scarlet Fever According to Total Number of White Blood Cells*

White Blood Cells per Cubic Millimeter	Percentage of Patients
Less than 10,000	31
10,000 to 12,000	22
12,000 to 14,000	17
14,000 to 16,000	13
16,000 to 18,000	9
18,000 to 20,000	4
20,000 to 30,000	3
30,000 to 40,000	1
	100

In all patients there was close uniformity in the measurements of the reaction when the reddened areas on both arms were compared. The degree of intensity of the initial eruption did not seem to be related to the results obtained on the Dick tests.

The total and differential white blood cell counts which were performed on the first day in the hospital revealed that 69 per cent of the patients had leukocytosis, the cell count being over 10,000 per cubic millimeter; 31 per cent had cell counts below 10,000. The majority of the patients had a leukocyte count of between 10,000 and 16,000 cells per cubic millimeter. In each patient polymorphonuclear cells predominated.

Thirty-three per cent of the patients showed an eosinophilia ranging from 5 to 27 per cent. Of the remainder, 25 per cent had from 3 to 5 per cent eosinophils and 42 per cent had 3 per cent or less.

The pronounced eosinophilia noted in several of the patients could not be accounted for by any complicating or associated disease. The scarlet fever in these patients did not appear to be exceptionally severe.

There was no correlation between the response to the Dick test and the total number of white blood cells or the percentage of eosinophils.

Desquamation occurred at some time during convalescence in 95 per cent of the patients. The intensity of the eruption and the degree of desquamation were definitely related. In the patients with a mildly or moderately intense erythema, desquamation was mild and often was limited to the hands and feet.

The throat cultures showed hemolytic streptococci in 85 per cent of the patients. Fifty-one per cent had 2 consecutive positive cultures, and for 34 per cent only the first of 2 successive cultures yielded the organisms. The remaining 15 per cent had negative cultures on both examinations.

TABLE 3.—*Distribution of Patients with Scarlet Fever According to Percentage of Eosinophils in White Blood Cell Count*

Percentage of Eosinophils	Percentage of Patients
3 or less	42
3 to 5	25
6 to 10	20
11 to 15	9
16 to 20	2
21 to 25	2

COMMENT

The period of observation on the patients in this study was limited to their stay in the hospital. No attempt is made to determine the value of the Dick reaction as a test of immunity or as an indication of recent or past infection.

It is assumed that the mechanism of the Dick test is on a toxin-antitoxin basis, similar in principle to the mechanism of the Schick test, and that the degree of reaction indicates a varying degree of susceptibility. On the other hand, several writers [1] considered the reaction of allergic origin, a positive reaction presupposing sensitization by streptococci. Recently, Rantz, Boisvert and Spink [2] reported that military recruits from areas with a low incidence of hemolytic streptococcic infections infrequently reacted to the Dick test. It was their conclusion that exposure to hemolytic streptococci and acquired hypersensitivity were probably essential for the development of a positive reaction. Their observations do not explain the high percentage of

1. Moriwaki, G.: J Prev. Med. **3**:13 (Jan.) 1929.

2. Rantz, L. A.; Boisvert, P. J., and Spink, W. W.: New England J. Med. **235**:39 (July 11) 1946.

positive initial reactions occurring in 59 per cent of our patients and the reversal in only 45.7 per cent.

The fact that the Dick reaction was negative in 14, or 93.3 per cent, of 15 patients who received scarlet fever streptococcus antitoxin points strongly toward a toxin-antitoxin mechanism. If sensitization plays any role in the reaction, it is probably a minor one. Allergic reactions to the Dick test are usually characterized by induration and, sometimes, by the appearance of a wheal. This type of response is more apt to occur after artificial immunization with scarlet fever streptococcus toxin. Any explanation of the reversal reactions to the Dick skin test must take into consideration a toxin-antitoxin mechanism. A change in a patient's reaction to the Dick test over a period of time is probably an indication of fluctuation of antitoxic immunity in that patient. The reactions of 6 of our patients became positive ten days after the negative reaction to the initial test but were again negative by the twentieth day. This type of reaction is difficult to explain by either the allergic or the immunologic mechanism.

The number of positive reactions in patients with active scarlet fever was surprisingly low, 59 per cent in our series. Gasul and Rhoads [3] obtained positive Dick reactions on the first day in 43.3 per cent of 30 patients with scarlet fever. It is felt that a single Dick test during the eruptive phase of scarlet fever is not of diagnostic value either in confirming or ruling out the presence of the disease. Since the serial study showed a reversal in reactions from positive to negative in only 45.7 per cent of our series, it cannot be stated that the reversal of the Dick reaction is a reliable diagnostic aid in this disease. This test apparently has no diagnostic value when the patient is treated with scarlet fever streptococcus antitoxin.

The eosinophilia has been described by others, but its importance as a diagnostic aid in scarlet fever is uncertain. Eosinophilia often accompanies conditions in which there is widespread involvement of the skin, and it has been described as a consistent finding in a number of cutaneous diseases.[4] The increase in eosinophils in scarlet fever, in all probability, represents a result of an extensive dermatitis which, in this case, is caused by an erythrogenic toxin. When the eosinophils in our patients were increased, that increase was moderate. The eosinophilia cannot be relied on as a diagnostic aid except as confirmatory evidence.

A fairly reliable diagnostic sign in scarlet fever is the presence of desquamation. However, desquamation may be absent or not apparent

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3. Gasul, B. M., and Rhoads, P. S.: Dick Test and Blood Agar Cultures as Aids in Diagnosis of Scarlet Fever, Am. J. Dis. Child. **49**:603 (March) 1935.

4. Kracke, R. R., and Garver, H. E.: Diseases of the Blood and Atlas of Hematology with Clinical and Hematologic Descriptions of the Blood Diseases, Philadelphia, J. B. Lippincott Company, 1937.

in those patients with a mildly intense erythema who present the problems in diagnosis.

The number of patients with hemolytic streptococci in the acute phase of scarlet fever is relatively high. Gasul and Rhoades [3] reported that the culture of material from the nose and throat and from surgical lesions yielded hemolytic streptococci in 100 per cent of patients with scarlet fever.

It appears that there is no single test which can be used alone for the diagnosis of scarlet fever. In the usual case the clinical evidence is sufficiently reliable for a correct diagnosis, but, when there is a faint or atypical rash, the diagnosis may be confirmed by the presence of hemolytic streptococci in the throat, leukocytosis, eosinophilia and, finally, characteristic desquamation of fingers and toes.

SUMMARY AND CONCLUSIONS

1. Review of the results of the Dick test alone in 100 patients studied proved it to be an unreliable test for diagnosis of scarlet fever.

2. An unusually high number of patients with scarlet fever showed a negative Dick reaction when tested within the first two days of the eruption.

3. Diagnosis based on the clinical signs was the most reliable of any single procedure.

4. Confirmation of the diagnosis of scarlet fever may be obtained by the leukocytosis, eosinophilia and presence of hemolytic streptococci in the throat and by the appearance of desquamation.

Front and Luzerne Streets (40).

ANTIPERTUSSIS SERUM (ANIMAL)

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CONTROLLED studies reported by Miller and Faber,[1] Kendrick and Eldering,[2] Sauer,[3] Singer-Brooks[4] and others[5] offer clinical evidence of the effectiveness of pertussis vaccine.

Bradford, Scherp and Brooks[6] showed that refined antipertussis serum, when injected into susceptible contacts, significantly diminished the clinical attack of whooping cough.

It was only natural that, if active immunity was to be established, passive immunity should be tried; for this reason a number of animal antitoxins were introduced for clinical treatment.

Mortality rates could not be used as criteria, since these rates had fallen in the past fifteen years, simply by good nursing care without any specific therapy, to 1.5 per cent, in the Department of Contagious Diseases, City Hospital, Cleveland.

From the Jack and Heintz Laboratory, Department of Contagious Diseases, City Hospital, and the Department of Pediatrics, Western Reserve University School of Medicine.

1. Miller, J. J., Jr., and Faber, H. K.: Immunization Against Pertussis, J. A. M. A. **112**:1145 (March 25) 1949.

2. Kendrick, P., and Eldering, G.: A Study of Active Immunization Against Pertussis, Am. J. Hyg., Sect. B **29**:133, 1939.

3. Sauer, L. W.: Whooping Cough, J. A. M. A. **112**:305 (Jan. 28) 1939.

4. Singer-Brooks, C.: A Controlled Study of Pertussis Prophylaxis, J. Pediat. **14**:25, 1939.

5. Silverthorne, N.: Active Immunization Against Whooping Cough, Canad. M. A. J. **41**:263, 1939. Doull, J. A.; Shibley, G. S.; Haskins, G. E.; Bancroft, H.; McClelland, J. E., and Hoelscher, H.: Active Immunization Against Pertussis, Am. J. Dis. Child. **58**:691 (Oct.) 1939. Howell, C.: Prophylactic Use of Pertussis Vaccine (Sauer), South. M. J. **31**:1166, 1938. Siegel, M.: Active Immunization Against Whooping Cough with Various Specific Vaccines, Am. J. Dis. Child. **56**:1294 (Dec.) 1938.

6. Bradford, W. L.; Scherp, H. W., and Brooks, A. M.: Prophylactic Value of Refined Antipertussis Rabbit Serum, Proc. Soc. Exper. Biol. & Med. **49**:157, 1942.

One patient ill with this disease cannot be compared with another. Each must be his own control and must be observed before and after treatment. There are several factors to be considered, such as the natural variability of the disease. Of 3 patients who are acutely ill in the early paroxysmal stage of whooping cough, all receiving the same type of symptomatic therapy, 1 may be clinically almost well within a week, another may gradually improve over a period of three weeks and the third may remain chronically ill for six weeks. We have seen all three types of these patients among those receiving no serum. Another factor is the stage of the disease when specific serum is given. If a child is admitted to the hospital late in the course of the disease, the serum might be given late enough so that improvement could be expected anyway. This, together with the fact that the patient gradually becomes better anyway, must make one skeptical.

Since there is no objective method of evaluation, the clinical results of the antiserum were determined by the appearance of the patient, whether he ate better and whether he coughed and vomited less after treatment than he did before.

In order to get a base line to determine the severity of the attack—how many times the patients coughed, how many times they vomited—patients were observed for twenty-four to forty-eight hours before being treated with serum.

Patients ill with whooping cough admitted to this hospital have had the disease at least seven days and usually are desperately ill on arrival.

The antipertussis serums used were products of several well known commercial firms. They were made of both rabbit and horse serums and were stated to be in doses of 10,000 to 99,500 units (unitage arbitrary) per vial. In addition to serum, chemotherapeutic agents and antibiotic substances were employed when necessary.

One hundred and twenty-four children between 1 month and 7 years of age were treated with serum. Serum was given in single doses of 1 vial a day, the total dosage varying from 1 to 4 vials and given in one to seven days.

The results obtained were graded good, fair and poor, on the basis of paroxysms, whoops and emeses, the general clinical course and the appearance of the patient. The response was considered good when there was a significant decrease in the number and the severity of paroxysms within forty-eight hours after the initial dose; fair, when the number and severity of paroxysms decreased within five to seven days after the final injection of serum, and poor when no effect was observed on their number and severity. There were many obvious errors of omission in the recording of the number of paroxysms, whoops and emeses. The general clinical effect proved to be more reliable as a factor of evaluation.

Twenty-nine patients received 1 vial; 25, 2 vials; 38, 3 vials, and 32, 4 vials of serum.

The responses following the administration of animal serums in the treatment of whooping cough were not so dramatic as those which followed the use of chemotherapeutic agents in other infections. The effect of antipertussis serum is unpredictable, but we feel that it is of some benefit. Several of the types of responses to the serum were as follows:

1. The number and severity of paroxysms, whooping spells and attacks of emeses decreased sharply in some instances.

2. With the decerase in the severity of the paroxysms, the patient's appetite was improved.

3. Despite little immediate or even no change in the number of paroxysms or emeses, in some patients there was a striking change in the general well-being, the behavior and the appetite.

There were observed a few patients in whom there was a temporary increase in the number of paroxysms after administration of the serum, with improvement taking place a day or so later. Occasionally, the impression was gained that the symptoms were aggravated for a period of eight to ten days after the use of certain serums.

One of the 124 patients (who received 321 injections of serum) had a serum reaction. This consisted of a pruritic, urticarious rash on the trunk and lower extremities and occurred ten days after the second of 2 injections of one of the antipertussis horse serums given on alternate days. The pruritis lasted three days.

In 3 children, there were unexplained fevers for twelve hours, six day and seven days, respectively, after one manufacturer's serum was given. In several infants, loose bowel movements developed coincidently with the serum injections, but, since many infants with whooping cough tend to have diarrhea, no significance could be attached to this finding.

In 42 patients, the results were good; in 36, fair, and in 40, poor. The reports on 6 patients were not completed for various reasons, such as discharge by release.

One vial of serum given in the paroxysmal stage did not alter the clinical course of the disease. It took 2 or 3 vials to give obvious results. The results in the last 64 patients treated during the first eleven days of the paroxysmal stage are as follows:

Of 55 of these children who received more than 1 vial of serum, 34 were in the early stage and 21 in the late stage. Of the 34 patients to whom more than 1 vial of serum was given early, 27, or 79.4 per cent, had a good or fair response. Of the 21 patients given serum late, 11, or 52.4 per cent, had a good or fair response.

COMMENT

The injection of a protein-like horse or rabbit serum is objectionable from an allergic standpoint, and the protection given is fleeting at best.

The cost of the serum should be considered.

The conditions in some persons seemed to be bettered on injection of the serum.

As to the question, "Is it worth while to inject serum?" anything is worth while when a patient is desperately ill, but the number of such patients is small, if one considers the present prophylactic use of penicillin and other antibiotic substances. The only type of patient to whom serum should be given is an infant desperately ill. The possibility that pertussis immune serum (human) might be more effective is being investigated. However, it will take fully a year before a report can be ready, but, from preliminary studies, the pertussis immune serum (human) seems to give even better results than animal antipertussis serum.

During the total period of this study, April 1946 to June 1948, there were 288 patients with whooping cough admitted to the Department of Contagious Diseases, City Hospital, Cleveland. These were also treated with the antiserum, and the results are similar. There were 4 deaths.

CONCLUSION

With consideration of the fact that the more seriously ill patients with whooping cough are usually the ones admitted to the hospital, and even with due credit to the efficiency of chemotherapeutic agents and antibiotic substances in controlling secondary infection, the record seems to indicate that animal antipertussis serum has some value in the treatment of the active disease.

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MUMPS MENINGOENCEPHALITIS WITH AND WITHOUT PAROTITIS

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ONLY recently and in few accounts have clinical and epidemiologic observations concerning mumps meningoencephalitis been confirmed by adequate diagnostic evidence from the laboratory, in spite of general recognition that clinical manifestations are not always pathognomonic. Kane and Enders [1] were the first to use serologic methods in a comprehensive study of the disease, and Henle and McDougall [2] demonstrated the ease of virus isolation. In the present study of 25 patients with mumps meningoencephalitis, 13 with no enlargement of the salivary glands, conclusions were based on cases diagnosed by means of a combination of the newer technics of serologic study [3] and virus isolation.[4] These methods provide important tools for a closer understanding of the biologic aspects of mumps infections. The patients presented were followed in two Boston hospitals [5] in 1948, a year particularly suited to the study because of the unusual prevalence of mumps in Massachusetts.

From the Department of Epidemiology, Harvard School of Public Health.

1. Kane, L. W., and Enders, J. F.: Immunity in Mumps: III. The Complement Fixation Test as an Aid in the Diagnosis of Mumps Meningo-Encephalitis, J. Exper. Med. **81**:137, 1945.

2. Henle, G., and McDougall, C. L.: Mumps Meningo-Encephalitis: Isolation in Chick Embryos of Virus from Spinal Fluid of a Patient, Proc. Soc. Exper. Biol. & Med. **66**:209, 1947.

3. (*a*) Robbins, F.; Kilham, L., and Enders, J. F.: The Antihemagglutination Test in the Diagnosis of Infections by the Mumps Virus, J. Immunol, **61**:235, 1949. (*b*) Enders, J. F., and Levens, J. H.: Mumps, in Diagnostic Procedures for Virus and Rickettsial Diseases, New York, American Public Health Association, 1948, p. 139.

4. Henle and McDougall.[2] Habel, K.: Cultivation of Mumps Virus in the Developing Chick Embryo and Its Application to Studies of Immunity to Mumps in Man, Pub. Health Rep. **60**:201, 1945. Levens, J. H., and Enders, J. F.: The Hemagglutinative Properties of Amniotic Fluid from Embryonated Eggs Infected with Mumps Virus, Science **102**:117, 1945. Leymaster, G. R., and Ward, T. G.: Direct Isolation of Mumps Virus in Chick Embryos, Proc. Soc. Exper. Biol. & Med. **65**:346, 1947.

5. The staffs of the John C. Haynes Memorial and of the Children's Hospital assisted in this study.

MATERIALS AND METHODS

Cerebrospinal fluid in amounts of 0.2 cc. was inoculated [6] into the amniotic sacs of 7 day old embryonated eggs, which were then incubated at 35 C. (95 F.) until the thirteenth day. The amniotic fluids were tested separately for the presence of virus by agglutination of hen erythrocytes. The result was confirmed by subsequent passage through eggs, using pooled amniotic membranes and fluids when hemagglutination was absent and only the fluid when hemagglutination occurred. No spinal fluid was judged free of virus until 3 egg passages were negative. Samples of saliva were centrifuged, treated with penicillin and streptomycin and examined in similar fashion. Strains of virus isolated by these methods were identified as mumps virus by the antihemagglutination test, using paired serums from patients known to have experienced a rise in mumps antibodies. Absence of growth in thioglycollate broth was used to eliminate the possibility of bacterial contamination in pooled egg materials. Paired serums from the patients of this series were tested for antibodies by mumps complement fixation [3b] and inhibition of hemagglutination.[7]

CLINICAL ASPECTS

The clinical reaction that characterized these 25 patients with mumps meningoencephalitis was similar to that reported in recent summaries.[8] Meningeal irritation was variously marked by headache, nausea, vomiting and nuchal rigidity. A few children had convulsions and delirium. One significant feature was the impossibility of distinguishing by clinical means between the signs and symptoms of patients with mumps meningoencephalitis and those of others who had serologically negative reactions for mumps and such clinical diagnosis as nonparalytic poliomyelitis [9] and lymphocytic meningitis.

Seven of 12 patients who had both meningoencephalitis and parotitis showed the two conditions on the same day. In 5 others parotid swelling preceded encephalitis five to nine days and had subsided by the time the patient came to the hospital.

A few patients had sequelae. One, $2\frac{11}{12}$ years of age, had weakness of the anterior part of the neck and abdominal muscles when seen later in a clinic for after-care of poliomyelitis. A 4 year old boy had weakness of a leg a few weeks after his discharge from the hospital.

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6. Kilham, L.: Isolation of Mumps Virus from the Blood of a Patient, Proc. Soc. Exper. Biol. & Med. **69**:99, 1948.

7. These tests were performed by the Research Division of Infectious Diseases, Children's Hospital.

8. Kane and Enders.[1] Eberlein, W. R., and Lynxwiler, C. P.: The Clinical Picture of Mumps Meningo-Encephalitis and Report of a Case Without Parotitis, J. Pediat. **31**:513, 1947. Brown, J. W.; Kirkland, H. B., and Hein, G. E.: Central Nervous System Involvement During Mumps, Am. J. M. Sc. **215**:434, 1948.

9. Kilham, L.; Levens, J. H., and Enders, J. F.: Nonparalytic Poliomyelitis and Mumps Meningoencephalitis: Differential Diagnosis, J. A. M. A. **140**:934 (July 16) 1949.

Two patients were judged to have personality changes as a result of their illnesses, these being especially striking in a boy, 16 years old. The patients of this series ranged in age from 1 to 35 years, with 18 under 10 years and 5 who were 16 years or older. Most of the patients were male, only 5 of the 25 being female. The average duration of illness was eight days.

Cerebrospinal Fluid.—A pronounced pleocytosis, with a high percentage of lymphocytes, characterized the spinal fluid of patients with

TABLE 1.—*Data on Patients with Mumps Meningoencephalitis with Parotitis**

		Cerebrospinal Fluid				Results of Serologic Tests			Mumps Virus Isolation	
Patient No.	Age, Yr.	Meningoencephalitis, Day	Leukocytes/ Cu. Mm.	Lymphocytes, per Cent	Total Protein, Mg./ 100 Cc.	Parotitis, Day	Antihemagglutination	Complement Fixation	Meningoencephalitis, Day	Cerebrospinal Fluid
1	5 10/12	3	152	96	17.4	3	1:128	1:64	3	0
						66	1:2,048	1:512		
2	7	8	960	100	145.0	3	1:32	1:32	3	+
		12	870	98	253.0	17	1:1,024	1:2,048		
3	3 6/12	2	1,050	96	36.0	9	1:32	1:64	2	+
						47	1:512	1:64		
4	7	2	210	100	—	4	1:32	1:4	6	0
						21	1:4,096	1:1,024		
5	4 5/12	3	143	100	23.4	3	1:256	1:16	—	—
		6	725	100	43.5	..	1:256	1:128		
6	6	2	140	100	30.0	6	1:128	1:512	5	+
		5	164	96	21.0					
7	5 6/12	3	2,230	98	76.3	11	1:32	1:16	4	0
		5	600	98	35.2	50	1:128	1:32		
8	8 6/12	4	195	98	—	5	1:32	1:4	4	0
		5	220	95	16.6	11	1:512	1:128	5	0
9	8	1	745	96	—	13	1:512	1:256	—	—
		3	630	99	143.5	26	1:1,024	1:1,024		
10	35	9	100	100	24.0	8	1:128	1:8	—	—
						31	1:512	1:128		
11	4 6/12	2	2,920	100	94.2	11	1:1,024	1:512	2	0
						27	1:4,096	1:2,048		
12	6	3	1,080	100	71.5	9	1:256	1:16	3	+
		11	10	100	26.7	16	1:2,048	1:256		

* A plus sign indicates virus isolation was successful, a zero that it was unsuccessful. A minus sign signifies th the test was not performed.

mumps meningoencephalitis (tables 1 and 2). Leukocytes exceeded 300 per cubic millimeter in 19 instances and were more than 1,000 per cubic millimeter in 9. No count fell below 100 per cubic millimeter in the first week of disease, and one reached a peak of 2,920 cells per cubic millimeter. Every patient showed a 95 or greater percentage of lymphocytes at some time, although 4 of the 64 spinal fluids examined had percentages slightly below this figure. The leukocyte count tended to reach a high point sometime during the first week of the disease (table 3). Several lumbar punctures were ordinarily needed to bring

TABLE 2.—*Data on Patients with Mumps Meningoencephalitis Without Parotitis**

Patient No.	Age, Yr.	Cerebrospinal Fluid: Meningoencephalitis, Day	Leukocytes/ Cu. Mm.	Lymphocytes, per Cent	Total Protein, Mg./ 100 Cc.	Results of Serologic Tests: Meningoencephalitis, Day	Antihemagglutination	Complement Fixation	Mumps Virus Isolation: Meningoencephalitis, Day	Cerebrospinal Fluid	Saliva
13	24	3	830	92	99.5	5	<1:32	1:32	5	0	—
		9	950	97	47.5	27	1:2,048	1:32			
14	4	4	2,100	90	37.9	6	<1:32	1:32	6	+	—
		15	392	100	—	20	1:1,024	1:512			
15	4	5	902	100	37.6	6	<1:32	1:64	6	+	—
						14	1:2,048	1:512			
16	5 6/12	5	690	100	64.2	4	<1:32	1:4	3	+	—
		33	103	100	68.0	12	1:4,096	1:512			
17	1 3/12	3	1,180	96	82.2	3	1:32	1:64	3	+	—
		12	86	96	120.8	18	1:256	1:512			
18	10	4	300	98	21.0	4	1:512	1:4	4	+	..
		8	371	100	62.4	21	1:4,096	1:64	5	..	0
19	6 6/12	3	530	95	41.1	3	1:128	1:16	3	+	..
		12	113	100	48.0	15	1:128	1:256	4	..	0
20	5 6/12	3	1,000	90	66.2	3	<1:32	1:32	3	+	0
		7	1,810	98	152.4	24	1:256	1:2,048			
21	2 11/12	3	159	96	19.2	3	<1:32	1:32	3	0	—
		5	232	100	38.4	15	1:512	1:512			
22	16	3	1,380	100	37.8	3	1:32	1:16	3	0	0
		15	80	98	41.7	29	1:256	1:128			
23	16	2	432	89	104.4	2	1:64	1:16	2	0	+
		8	200	90	39.8	26	1:2,048	1:128	4	..	+
24	1 8/12	4	1,460	98	72.6	5	1:32	1:32	—	—	—
		11	145	100	63.6	13	1:512	1:512			
25	24	5	804	100	40.4	3	<1:32	1:4	5	+	—
		11	512	100	—	5	<1:32	1:8			

* For explanation of symbols, see footnote to table 1.

TABLE 3.—*The Cerebrospinal Fluid in a Patient with Mumps Meningoencephalitis (Patient 16)*

Day of Disease	Leukocytes/ Cu. Mm.	Lymphocytes, per Cent	Total Protein, Mg./100 Cc.
3	310	100	30.4
5	690	100	64.2
10	426	100	112.4
13	412	100	118.8
18	298	100	88.0
21	240	100	77.0
24	120	100	70.6
27	74	100	73.6
31	94	100	78.8
33	103	100	68.0

out maximum values both for leukocytes and for total proteins. Maximum values for total proteins usually came later than those for leukocytes. Proteins were above 40 mg. per hundred cubic centimeters in 16 patients; 6 had values greater than 100 mg., and patient 2 had 253 mg. on the twelfth day (table 1). Leukocytes and total proteins of spinal fluids often persisted at abnormal levels after clinical recovery, in 4 patients for two weeks and more after onset and in patient 16, past the thirty-third day.

SEROLOGIC REACTIONS

The antihemagglutination and the complement fixation tests gave comparable results (tables 1 and 2). One or both tests showed a four-

TABLE 4.—*Data on Patients with Infections of the Central Nervous System Other Than Mumps**

Patient No.	Age, Yr.	Cerebrospinal Fluid: Disease, Day	Leukocytes/Cu. Mm.	Lymphocytes, per Cent	Total Protein, Mg./100 Cc.	Serologic Reactions: Disease, Day	Antihemagglutination	Complement Fixation	Mumps Virus Isolation: Disease, Day	Cerebrospinal Fluid	Diagnoses
26	8	7	1,380	80	127.0	7	1:128	1:64	9	0	Acute encephalitis
		15	138	92	96.0	28	1:256	1:64			
27	12	2	160	96	48.8	6	1:256	1:16	7	0	Lymphocytic meningitis
		3	337	98	37.6	12	1:512	1:16			
28	10	3	19	84	36.0	22	1:4,096	1:512	4	0	Encephalitis
		4	20	95	38.4	57	1:8,192	1:512			
29	12	4	924	25	112.5	4	1:1,024	1:128	4	0	Paralytic poliomyelitis
		7	80	96	54.4	21	1:1,024	1:128			
30	19	3	8	95	30.2	4	1:256	1:64	3	0	Paralytic poliomyelitis
		10	3	100	19.9	15	1:256	1:64			
31	5	5	150	90	41.5	6	<1:32	<1:4	6	0	Postmeasles encephalitis
		6	141	95	....	15	<1:32	<1:4			

* For explanation of symbols, see footnote to table 1.

fold and usually a greater increase in antibodies when serums of the acute and convalescent phases were compared for all patients, except for patient 25, for whom serums from only the acute stage of illness were available. The first serum for this patient had a low titer of complement fixing antibodies but showed a twofold rise after two days and mumps virus was isolated from the spinal fluid. Patients 5 and 19 showed a substantial rise of antibody titer by complement fixation test, while both acute and convalescent phase serums had identical titers by the antihemagglutination test. The reverse situation is illustrated by the titers of patients 3 and 13. The times at which antibody rises took place varied so greatly from patient to patient as to give no definite indication that one type of antibody rose in titer earlier than the other.

Among patients with encephalitis serving as controls (table 4) by reason of clinical differences in some and the uniform failure to isolate mumps virus, a number showed high titers of mumps antibodies in

both acute and convalescent phase serums. A few might have shown a significant rise of mumps antibodies had the serums been collected at different intervals than they were. Spinal fluids of patients 26 and 27 were not unlike those of patients with proved mumps infections. Two patients with paralytic poliomyelitis also had high, unchanging titers of mumps antibodies, especially patient 29, who had a history of exposure to mumps,

Patient 28 was unusual in that encephalitis appeared three weeks after parotitis. Serums from this patient collected three and six weeks after the onset of parotitis expectedly showed high antibody titers. The condition was not considered to be primary mumps meningoencephalitis because (1) the spinal fluid was unlike that of patients with proved mumps encephalitis, (2) for encephalitis to follow parotitis after three weeks is unusual, (3) the patient came from a locality where an outbreak of mild meningoencephalitis of known origin was prevalent and the spinal fluid was typical of those observed in the course of the epidemic and (4) attempts to isolate mumps virus from the spinal fluid were unsuccessful. A secondary or postinfectious type of encephalitis, however, is conceivable.

ISOLATION OF MUMPS VIRUS

Of 21 attempts to isolate mumps virus from patients with clinical mumps meningoencephalitis, all were successful. An initial belief that the first two or three days of the disease were most favorable for isolation of virus was not substantiated, since 4 strains were obtained on the fifth and sixth days when the proportion of failures was no greater. The persistence of an abnormal spinal fluid (table 3) suggests that mumps virus could be isolated from the spinal fluid occasionally in the second week of disease or even later, but this was not determined, since, other than one specimen taken on the eleventh day, which proved negative, no specimens for virus isolation were collected after the sixth day. All spinal fluids were subjected to at least 3 passages in embryonated eggs. Mumps virus appeared on the first passage in 5 instances, on the second passage in 4 and on the third passage, twice. Six attempts to demonstrate mumps virus directly in the spinal fluid by agglutination of hen erythrocytes were unsuccessful. The mumps virus in cerebrospinal fluid can withstand storage under dry ice for long periods, since the fluid of patient 25 yielded virus five months after first refrigeration.

Patient 23 was of special interest, since mumps virus was isolated from the saliva on the second and fourth days of disease, in spite of an absence of enlargement of the salivary gland, although orchitis developed

on the sixth day. Virus was not isolated from 4 other patients having no enlargement of the salivary glands when specimens were collected on the third to fifth days of disease.

To test the hypothesis that invasion of the central nervous system is a primary feature of mumps infections, spinal fluids from 6 patients with early mumps parotitis and no evidence of meningeal involvement were examined for virus. The series of 3 egg passages made with each specimen gave a negative result.

A total of 12 patients served as controls for the group with serologically proved mumps meningoencephalitis: 6 patients with uncomplicated mumps parotitis and 6 with disease of the central nervous system determined not to be mumps by serologic test. Mumps virus was isolated from the spinal fluid of more than half of the patients with confirmed mumps infection of the central nervous system and in no instance from that of the control series.

EPIDEMIOLOGIC FACTORS

The cases reported all occurred between March and November 1948, a year in which mumps was unusually prevalent in Massachusetts. Cases of meningoencephalitis associated with parotitis were scattered more or less regularly throughout the period, but 11 of the 13 patients with meningoencephalitis and no parotitis were seen from mid-May to early September. As the numbers are small, they may represent no more than chance distribution. The hypothesis is suggested, however, that enlargement of the salivary glands is a less frequent manifestation of mumps in summer than in winter. Johnson and Goodpasture,[10] in the course of three years, found it difficult to induce parotitis in monkeys during the summer months. This may well be a factor in the rapid decrease of reported cases of mumps in warm weather, as mumps infection without glandular enlargement is difficult to recognize clinically. This absence of enlargement would have epidemiologic significance in explanation of the manner in which mumps virus is carried over in a population from one period of seasonal prevalence to another. Support for such an hypothesis requires further field and laboratory studies.

One might postulate an especially neurotropic strain of the mumps virus as responsible for an excess prevalence of simple meningoencephalitis that is presumably communicable. In all probability, the spread of mumps infection is not wholly by patients with parotid swelling. Mumps virus was isolated from 2 successive samples of saliva

10. Johnson, C. D., and Goodpasture, E. W.: Experimental Immunity to the Virus of Mumps in Monkeys, Am. J. Hyg. **23**:329, 1936.

from patient 23 in the absence of enlargement of the salivary glands. A 16 year old boy (patient 22) showed simple mumps meningoencephalitis in August, three weeks after his 15 year old sister had an illness characterized by fever, apathy, headache and delirium of a week's duration and two weeks after a younger sister experienced a similar illness. In none of the children was salivary gland enlargement observed. However, 10 of the 13 patients with simple meningoencephalitis had a history of exposure to mumps parotitis three to four weeks before onset. There is little factual evidence that mumps virus shows strain variations.

COMMENT

Mumps meningoencephalitis, with or without parotitis, is in certain years a common form of lymphocytic meningoencephalitis among children and young adults. Knowledge of the true incidence of this disease, especially when no glandular swelling is apparent, will await further application of newer diagnostic methods to a study of epidemics of mumps occurring within closed groups. No other encephalitis can be identified more readily by serologic methods, for the antihemagglutination test is simple and as satisfactory as complement fixation in establishing a diagnosis of mumps.[3a] A serologic test is indicated whenever appropriate signs and symptoms are associated with a spinal fluid having 150 to 2,500 leukocytes per cubic millimeter, of which 95 per cent are lymphocytes, and an elevated total protein content and, especially, with a history of exposure to mumps. These grouped findings are characteristic but not pathognomonic of mumps meningoencephalitis. Exceptions are few, either in the present series or in the fully substantiated cases of others.[11] Full confirmation of mumps meningoencephalitis is believed to rest on (1) the presence of abnormal cerebrospinal fluid findings and (2) a fourfold or greater increase of mumps antibody when serum from the acute phase is compared with specimens taken in convalescence. Successful isolation of mumps virus gives additional confirmation. Demonstrated abnormalities in the spinal fluid are important, since clinical findings, such as drowsiness, headache, nausea and vomiting, occur in other conditions apart from a true encephalitis. A high titer of mumps antibody in a single convalescent phase serum may be misleading. Some patients of this series, who clinically did not have mumps, had a uniformly high level of antibody in both acute and convalescent phase serums. Acute phase serum should be obtained as early as possible, preferably within a few days of onset, because mumps antibodies are often present when active symptoms first appear.

Virus isolation from cerebrospinal fluid has been accomplished in only a few types of encephalitis of known origin. It has been demon-

11. Kane and Enders.[1] Henle and McDougall.[2]

strated here, however, that virus can be isolated in 50 per cent or more of spinal fluids taken in the first week of mumps meningoencephalitis. Whether mumps virus increases quantitatively in the spinal fluid during the first week of disease or is most prevalent at the onset is not known. Virus is demonstrable in almost all samples of saliva collected early in the course of mumps parotitis.[12] It is likely, therefore, that something more than inadequacy of technic is needed to account for failure to demonstrate mumps virus in salivas from 4 to 5 patients tested who had meningoencephalitis without parotid swelling. Another explanation is advanced later.

Mumps parotitis can be either apparent or inapparent. The case of patient 23, in which mumps virus was isolated from 2 successive samples of saliva collected when careful clinical observation revealed no enlargement of salivary glands, presents evidence of the existence of inapparent parotitis. Henle and his co-workers[13] also demonstrated this condition by isolation of virus from the saliva of children with artificially induced mumps. In the absence of more complete information, a working hypothesis is advanced regarding its frequency and relationships. Thus, an inapparent parotitis can in some patients precede, in others accompany, meningoencephalitis as apparent parotitis does. In a number of patients presented in this report, a preceding parotid swelling had completely subsided by the time of admission to the hospital for encephalitis. Similar behavior by inapparent parotitis running its course prior to the onset of encephalitis explains the reason samples of saliva from patients 18, 19, 20 and 22 (table 2) were collected too late to contain demonstrable virus. Isolation of virus from the saliva of patient 23 was favored by the simultaneous occurrence of inapparent parotitis and encephalitis. A further hypothesis is that involvement of the salivary glands, with or without swelling, is a primary feature of all types of mumps infection. Confirmation, or disproof, of these hypotheses awaits further investigation into the pathogenesis of mumps.

CONCLUSIONS

Mumps meningoencephalitis is possibly one of the commoner types of encephalitis occurring in certain years, as suggested by 25 patients, 13 without parotitis, observed in two Boston hospitals in 1948. As clinical findings are not sufficiently characteristic, mumps meningoencephalitis without glandular enlargement is to be recognized with certainty only

12. Kilham, L.: To be published.

13. Henle, G.; Henle, W.; Wendell, K. K., and Rosenberg, P.: Isolation of Mumps Virus from Human Beings with Induced Apparent or Inapparent Infections, J. Exper. Med. 88:223, 1948.

through demonstration of a significant rise of specific antibodies when acute and convalescent phase serums are compared, unless mumps virus is isolated from the spinal fluid. Serologic diagnosis is readily accomplished by means of a relatively simple antihemagglutination test.

In some instances, mumps virus is demonstrable in the cerebrospinal fluid as late as the sixth day of encephalitis and occasionally from saliva in patients with meningoencephalitis unaccompanied by enlargement of salivary glands.

Mumps meningoencephalitis may be prevalent throughout the summer months. There is a suggestion that enlargement of the salivary glands is less frequent at this season.

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CONGENITAL ANOMALIES FOLLOWING MATERNAL RUBELLA

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GREGG [1] reported in 1941 a series of 78 cases of congenital cataract and other congenital anomalies in children whose mothers gave a history of rubella in early pregnancy. Numerous reports and surveys [2] have confirmed Gregg's theory of a causal relationship between this maternal infection and the anomalies of the child. Gregg's basic discovery has led to a number of secondary questions which have not yet been answered satisfactorily.

In the first publications, Gregg pointed out that in Australia the rubella epidemic of 1940 which had affected the mothers of children with cataract and other anomalies was of unusual severity and was accompanied with complications rare in the course of ordinary "German measles." He was so impressed by the swelling of the glands of the neck, the sore throat, the involvement of the wrist and ankle joints

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1. Gregg, N. M.: Congenital Cataract Following German Measles in the Mother, Tr. Ophth. Soc. Australia (1941) **3**:35-46, 1942.

2. (*a*) Swan, C.; Tostevin, A. L.; Moore, B.; Mayo, H., and Black, G. H. B.: Congenital Defects in Infants Following Infectious Diseases During Pregnancy, with Special Reference to Relationship Between German Measles and Cataract, Deaf Mutism, Heart Disease and Microcephaly, and to Period of Pregnancy in Which Occurrence of Rubella Is Followed by Congenital Abnormalities, M. J. Australia **2**:201-210 (Sept. 11) 1943. (*b*) Gregg, N. M.; Beavis, W. R.; Heseltine, M.; Machin, A. E.; Vickery, D., and Meyers, E.: Occurrence of Congenital Defects in Children Following Maternal Rubella During Pregnancy, ibid. **2**:122-126 (July 28) 1945. (*c*) Swan, C., and Tostevin, A. L.: Congenital Abnormalities in Infants Following Infectious Diseases During Pregnancy, with Special Reference to Rubella: Third Series of Cases, ibid. **1**:645-659 (May 11) 1946. (*d*) Wesselhoeft, C.: Medical Progress: Rubella (German Measles), New England J. Med. **236**:943-950 (June 19); 978-988 (June 26) 1947. (*e*) Swan, C.: Congenital Malformations in Infants Following Maternal Rubella During Pregnancy: A Review of Investigations Carried out in South Australia, Tr. Ophth. Soc. Australia (1944) **4**:132-141, 1946.

and the general constitutional disturbance observed in that epidemic that he expressed doubt concerning the correctness of the diagnosis.

> Running concurrently with this epidemic were the epidemics of sore throat known as Ingleburn throat or Puckapunyal throat et cetera, deriving its name from the military camp with which it was associated. These epidemics started in the camps and spread to the civilian population. Could they not have been streptococcal in origin and is it not possible that the rash diagnosed as "German measles" may have been, in some cases, a toxic erythema accompanying a streptococcal infection? [1]

When it was shown that the predominant organism in the throat was Hemophilus influenzae and that there was no correlation between the sore throats and the congenital anomalies, Gregg, as well as Swan and his co-workers,[2a] became convinced that the maternal disease was rubella. But they considered the possibilities that only severe forms of this disease resulted in defects in the child or that a change in the virulence of the rubella virus had occurred. These considerations were prompted by early workers who questioned that such an obvious correlation between a maternal disease and anomalies in the offspring could have been missed by the medical profession up to that time. It was thought that perhaps medicine was confronted with a new phenomenon. As Swan [2e] expressed it:

> In view of the universal occurrence of German measles, it seems curious that if congenital defects frequently followed a maternal attack during pregnancy, the connextion between the two conditions was not discovered earlier.

This question should be of particular interest to pediatricians who are well acquainted with rubella, who are not infrequently called in consultation to see adult patients with the disease and who should have examined many defective children of the type described by Gregg.

Observations made in the Pediatric Department of the University of Cincinnati College of Medicine may contribute answers to some of these secondary questions. We have been acquainted with the work of Gregg [1] and Swan and his associates [2a] since 1943. Early in 1944 Dr. Laura Bickel,[3] wrote us about 4 cases of congenital cataract and defect of the interventricular septum which she had seen in Houston, Texas. In 3 of these cases the mother had had rubella during early pregnancy. This observation indicated that the syndrome described by Gregg occurred also in the United States; this was shortly followed by reports of Erickson [4] and Reese,[5] who had seen similar cases in this country. The staff of the Pediatric Department of the University of

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3. Bickel, L.: Personal communication to the authors.

4. Erickson, C. A.: Rubella Early in Pregnancy Causing Congenital Malformations of Eyes and Heart, J. Pediat. **25**:281-283 (Oct.) 1944.

5. Reese, A. B.: Congenital Cataract and Other Anomalies Following German Measles in the Mother, Am. J. Ophth. **27**:483-487 (May) 1944.

Cincinnati has been acquainted with the prenatal rubella syndrome since about that time. While no special search was made for cases of this type, it is not likely that many patients with the typical syndrome passed through the hospitals and clinics of the department unnoticed. From 1944 to the end of 1948 the following cases which bear a relationship to this syndrome have been seen in the department.

REPORT OF CASES

CASE 1.—*Deafess, mental retardation, athetosic movements and petit mal epilepsy in a girl whose mother had rubella in the sixth week of pregnancy. The infection was acquired during an epidemic of rubella in 1936.*

S. H., a white girl, was born Oct. 2, 1936, weighing less than 5 pounds (2,268 Gm.), although the period of gestation was nine months and ten days. The mother was told that the baby was blue for one-half hour after birth, but the obstetrician attributed this fact to the position of the cord around the neck at the time of birth. Athetosic movements were first observed at 4 months of age. Deafness was noted in the child at 4 to 6 months of age. The child did not crawl until 1 year nor did she walk until 2 years of age. She never learned to talk and was placed in a private school because of the deafness, the athetosic movements and the mental slowness. She was brought to our clinic when 9 years of age.

The family history disclosed that the son of a half sister of the maternal grandfather had had congenital spastic paralysis. No other congenital abnormalities were known to exist within the family. The father, a teacher, was living and well. One sibling, born in 1933, was living and well. They, as well as the mother, were intelligent and exhibited no abnormalities. The mother's last menstrual period in the winter of 1935–1936 was on Dec. 15, 1935. Six weeks later she contracted rubella. There was an epidemic of the disease in the community at that time. The remainder of the pregnancy, which resulted in the birth of S. H., was uneventful.

Physical examination of S. H. in 1945 revealed her to be a well developed and well nourished girl with complete deafness and mutism. Neurologic examination disclosed the presence of athetosic movements and many attacks of petit mal epilepsy daily. She had no cataracts or signs of congenital heart disease. Psychometric testing revealed a mental age of 3 years 3 months and a social quotient of 34 on the Vineland Social Maturity Scale. Stanford-Binet testings disclosed a mental age of 3 years 6 months and an intelligence quotient of 37 (Dr. Doris T. Allen).

This case indicates that in an epidemic of rubella in 1936 the embryo of a mother who had the disease in the sixth week of pregnancy was injured, with the result of congenital deafness, mental retardation and possibly other neurologic manifestations.

That the connection between maternal rubella and congenital defect of the offspring is not new is borne out by 2 other cases of which we have knowledge. These patients were not seen in the Pediatric Department of the University of Cincinnati, but, since they are of great interest and have not been reported elsewhere, we include them in this communication.

CASES 2 and 3.—*Bilateral cataracts, congenital heart disease, deafness, microcephalia and mental retardation, followed by epilepsy and glaucoma, in unlike-sexed twins whose mother had had rubella during the third week of pregnancy in 1930.*

The X twins were born on Dec. 27, 1930. They were unlike-sexed, white twins, born after a gestation of seven and two-thirds months, weighing 3½ pounds (1,587.6 Gm.) each. There was deafness following scarlet fever in a great-grandmother, but none of the other defects observed in the twins had occurred in members of either side of the family for five generations. The mother was 25 years old when the twins were born. She had had rubella in the third week of pregnancy. The diagnosis may be considered established since the mother was under close medical observation. Congenital cataracts were recognized immediately in the girl and at the age of 2 months in the boy. Both children were deaf and had moderate microcephalia. Both had congenital heart disease. Epilepsy developed in both later in life, and the boy had glaucoma which was not well controlled by operation. At the age of 17 years it was estimated that their mental development did not exceed the 3 year level. An accurate evaluation of the mentality was difficult because of impaired hearing and vision.

These cases demonstrate that the prenatal rubella syndrome existed as early as 1930. They are also of interest because a pair of non-identical twins were equally affected by the prenatal infection.

CASE 4.—*Deafness in a boy whose mother had had rubella in the fourth month of pregnancy.*

R. D., a white boy, was born on Oct. 26, 1943, following a gestation period of nine months. The weight at birth was 6 pounds 13 ounces (3,090.1 Gm.). The child was brought to our clinic at 3½ years of age with the complaint of deafness and inability to speak. He had had no serious illnesses since birth.

A study of the family history showed no deafness on either the maternal or the paternal side. There was no consanguinity between the mother and the father. The mother was 19 years of age at the time of the child's birth. The mother stated that her only illness during pregnancy occurred in the fourth month. At that time a rash with fever was diagnosed as rubella by her physician.

Physical examination of R. D. at 3½ years of age revealed extreme deafness, as evidenced by tuning fork and voice tests. Hypoactive labyrinths were found bilaterally on caloric equilibrium tests (Dr. W. C. Thornell). The child was able to say only one word, "mama." No other physical abnormalities were discovered. The child's mental status was difficult to evaluate, but he performed simple problems with blocks well and responded quickly to directions given by the mother by motions of her hands.

CASE 5.—*Congenital heart disease, partial deafness, speech defect and probable mental retardation in a boy whose mother had had rubella in about the fourth week of pregnancy.*

L. P., a white boy, was born at term on Jan. 19, 1944, weighing 7 pounds 1 ounce (3,203.5 Gm.). No abnormalities were noted at birth. The child sat up at 6 months, walked at 12 months and seemed to progress normally except that he did not talk until he was 3½ years old. He was referred to our clinic because of this speech difficulty.

The family history disclosed no abnormalities in either the maternal or paternal families. An older sister of L. P. was normal. This older sister had

an attack of rubella in the middle of April 1943, and the mother contracted the disease about two weeks later. The mother felt that her attack of rubella came about three or four weeks after her last menstrual period in 1943, which started April 4.

Physical examination at 3½ years of age showed a boy small for his age whose eyes were normal. A slight bulging deformity of the chest was present. A loud murmur was heard over the left side of the chest, with a thrill in the third left interspace. Partial deafness, particularly to low-pitched notes, was discovered. A moderate speech defect, possibly due to deafness, was present. No psychometric testing was done, but the limited vocabulary and the failure to respond to simple testing left an impression of mental retardation.

CASE 6.—*Congenital deafness, congenital heart disease, spina bifida occulta and small head in a boy whose mother had an exanthem (probably rubella) in the fourth to sixth weeks of pregnancy.*

W. L. P., a white boy, was born at term on Dec. 8, 1944. His weight at birth was 5 pounds 13 ounces (2,636.5 Gm.), delivery being uneventful. When the child was 4 months of age, his private physician suspected that microcephalia was present. The child sat up at 8 months of age. When the boy was 10 months old, his parents noticed for the first time that he was partially deaf. He began walking at 19 months. He was seen in our clinic for evaluation at the age of 2½ years.

No congenital anomalies had been noted in the family. One brother 6 years of age was living and well. His father and mother were normal. The mother claimed that she had had measles twice as a child. Her last menstrual period in 1944 was in February. Late in March 1944, the mother had "measles," according to her, for the third time. From her description this was probably rubella. No other illness occurred during the pregnancy.

Physical examination of W. L. P. in May 1947 revealed the following data: His weight was 24½ pounds (11.1 Kg.) and his height, 34¼ inches (87.6 cm.). The circumference of the head was 17½ inches (44.5 cm.). The hearing was definitely impaired. The number of words which he could speak intelligibly was limited. A roentgenogram disclosed an enlarged heart, measuring 8 cm. in a chest of 14.5 cm., with a prominence in the region of the pulmonary conus. A murmur over the precordium aroused suspicion of the presence of a septal defect. Spina bifida occulta was revealed through roentgenographic examination. No rating of intelligence was made because of hearing and speech difficulties, but the child seemed fairly intelligent.

CASE 7.—*Partial deafness and pectus excavatum in a child whose mother had rubella and mumps in the third month of pregnancy.*

E. E., a white boy, was born on July 7, 1943, weighing 2 pounds 1 ounce (935.5 Gm.), after a gestation period of six months. The child was brought to our clinic because of deafness at the age of 4½ years.

The family history disclosed no known cases of deafness in the maternal or paternal families. The father, 19 years of age, and the mother, aged 18 years, were healthy at the time of the birth of E. E. Conception probably took place in late January 1943, the mother's last mentrual period having begun January 20. In April 1943 the father contracted rubella. One week later the mother had the same symptoms and a diagnosis of rubella was made by her physician. One week after recovery the mother contracted mumps.

Physical examination of E. E. in our clinic on Feb. 28, 1948, revealed the following: His weight was 31¾ pounds (14.4 Kg.), which is approximately

6 pounds (2.7 Kg.) below average for his age. His height was 39 inches (99 cm.). Partial deafness was present. The chest showed pectus excavatum, but congenital heart disease could not be established. His mental development was apparently normal.

CASE 8.—*Spastic diplegia, congenital heart disease, choroidal degeneration and partial deafness in a child whose mother had had rubella in the second month of pregnancy.*

P. M., a white boy, was born at term on Dec. 13, 1942. His weight at birth was 5 pounds 6 ounces (2,438 Gm.). Cyanosis was noted at birth but disappeared soon after repeated stimulation. He took feedings poorly in the first few weeks, apparently having difficulty in swallowing. He was described as being extremely limber during the first six months of life and did not sit alone until 9 months of age. Verbalizing began at 12 months; walking commenced at 20 months, at which time a peculiar spastic gait was noted. When the boy was 2 years of age, the parents were told by several physicians that the child had some hearing difficulty and heart disease. When 40 months of age, the child was brought to our hospital for orthopedic evaluation of his spastic gait.

Neither the maternal nor the paternal family history revealed any cases of congenital abnormalities. The father, 27 years of age, and the mother, aged 28 years, were healthy and normal at the time of the child's birth. The mother had a definite but mild case of rubella in the second month of pregnancy.

At 40 months of age the child was within normal limits for height and weight. Examination of the chest revealed a loud systolic murmur and thrill in the second and third interspaces to the left of the sternum of the type heard in persons with interventricular septal defects. A roentgenogram of the heart revealed no enlargement, and an electrocardiogram showed no abnormalities. There was slight spasticity of the lower extremities resulting in a spastic gait. Choroidal degeneration was noted on ophthalmoscopic examination. During his stay in the hospital repeated examinations disclosed slight deafness. The child's speech was intelligible, and it was the opinion of several observers that the mental development was normal.

CASE 9.—*Congenital deafness and congenital heart disease in a girl whose mother had an exanthem (probably rubella) in the second or third month of pregnancy.*

J. H., a Negro girl, was born on Dec. 26, 1945, after a gestational period of nine months. Her weight at birth was 4 pounds 10 ounces (2,097.9 Gm.). The mother noticed early that the child did not hear. Her development was good otherwise, but she remained small and underweight. She sat up at about 7 months and walked at 10 months, and toilet training was accomplished at about the same time. The first teeth erupted at 10 months. The mother thought that the child was bright but did not hear.

The child had two younger brothers who were said to be normal. According to the mother, there was no deafness or congenital heart disease in the family. The parents were not consanguineous. The mother was 16 years old when pregnant with the patient. In the second or third month of pregnancy she had a rash which she considered as measles. No physician was called. She felt sick and "broke out real red." Her eyes watered. She did not remember whether she had fever or cough.

Physical examination in November 1948 revealed the following data: The weight was 23 pounds (10.4 Kg.) and the height, 33¾ inches (85.7 cm.); the

circumference of the head was 17½ inches (44.5 cm.). She gave the impression of a small but well proportioned child. Hypertelorism was present and a slight strabismus was noticeable. The media and fundi were normal. She was obviously deaf. A loud systolic murmur was audible to the left of the sternum and transmitted to the left subclavicular area. The size and shape of the heart appeared normal on fluoroscopy. The presence of a defect of the interventricular septum or an open ductus arteriosus was suspected. She understood orders given by her mother in spite of her deafness and appeared mentally normal.

CASE 10.—*Cleft palate in a girl whose mother had rubella in the fourth week of pregnancy.*

J. E., a white girl, was born at term on Feb. 7, 1944. The delivery was normal and spontaneous. The child weighed 5 pounds 4 ounces (2,381.4 Gm.). A cleft of the posterior portion of the palate was noticed at birth.

The parents and grandparents were not consanguineous. With the help of the parents, a pedigree was drawn up which included 103 blood relatives. No cleft palate or harelip occurred in any of the members charted. The patient was the only child of healthy parents. The father at the time of the child's birth was 25 years old and the mother 22 years old. The mother's eating habits were irregular for six months prior to pregnancy. Her last menstrual period was April 12, 1943. Conception took place between April 26 and 30. The mother was exposed to her sister and niece who had rubella beginning in the period April 27 to 30. The first symptoms of rubella appeared in the mother on May 18 when she was about twenty-two days pregnant. The disease consisted of a rash, fever and malaise. The diagnosis of rubella was made by physicians in the mother, as well as in her relatives to whom she had been exposed.

J. E. was seen in the Children's Hospital at the age of 3 years. At that time she returned for a second operation for closure of a cleft in the posterior part of the palate. She had no harelip nor alveolar clefts. There was a slitlike opening in the posterior third of the palate extending through the soft palate. She had no cataracts and had good vision and hearing. There was no evidence of a congenital cardiac lesion or of mental retardation.

CASE 11.—*Congenital heart disease, bilateral cataracts, small head and mental retardation in a boy whose mother was exposed to rubella at the end of the fifth gestational week without awareness of having had rubella or any other disease during pregnancy.*

R. T., a white boy, was born at term on Jan. 5, 1944. The delivery was normal and spontaneous. The weight at birth was 7 pounds (3,175.1 Gm.). No abnormalities were noted at birth, but at 10 weeks of age cataracts were seen in the child.

The father was 43 and the mother 35 years old at the time of the child's birth. The father was an orphan, but to his knowledge there were neither cataract nor heart disease in his family. The mother knew of no person with cataracts in her family. She could not remember ever having rubella. Two older children, born in 1935 and in 1937, were living and well. The mother again became pregnant in 1943, her last menstrual period beginning April 6, 1943. In the middle of May 1943, when the mother was about five weeks pregnant, her two older children had rubella. The mother cared for her children during this period but did not show a rash or other symptoms of illness herself.

R. T. was seen in the Children's Hospital at the age of 16 months. He had bilateral cataracts, with constant roving and searching movements of the eyes.

A systolic murmur was heard over the whole precordium, being loudest at the apex and extending upward along the sternum to the third and second left interspaces. His hearing was normal. The circumference of the head was 16¾ inches (42.6 cm.); his height was 29 inches (73.7 cm.), and his weight was 16 pounds 10 ounces (7,541 Gm.). The child was unable to walk. A teleroentgenogram of the chest disclosed the greatest cardiac width to be 6.5 cm. in a chest of 13 cm., without the configuration indicative of heart disease. The serologic reaction was negative. At 2 years and 3 years of age the child's cataracts were needled, procedures which resulted in improvement in vision. At this time it was felt that the child was definitely mentally retarded.

CASE 12.—*Bilateral cataracts, small head, mental deficiency and questionable heart disease in a child whose mother was exposed to rubella during the second month of pregnancy. The mother remembers having had a mild infection of the upper respiratory tract with malaise subsequently, but in the absence of rash it cannot be said that she had rubella.*

B. F. H., a white girl, was born at term on Aug. 15, 1944, the thirteenth of 14 children. The child was born at home and weighed approximately 6 pounds (2,721.6 Gm.). She was referred to our clinic on Nov. 17, 1947 because of blindness.

The 13 brothers and sisters of this child were normal. The paternal grandmother had had senile cataract at the age of 66 years. No other members of the family had been known to have cataracts. A half sibling of the mother, who died at the age of 9 years, had been a deaf-mute. There was no further history of anomalies in the family. The mother did not recall having had rubella at any time. Later, however, it was established that in December 1943, during the second month of her thirteenth pregnancy, she had taken care of one of her children who had rubella. In the following week she was not well and had signs of a mild infection of the upper respiratory tract with sore throat, malaise and pains in the neck. To her knowledge, she had no rash or fever at that time.

The patient, at the age of 3½ years, showed bilateral cataracts which were said to be congenital. A soft systolic murmur, rather short in duration, was heard in the first and second left interspaces. The murmur varied in intensity with respiration and position, so that whether it was due to a congenital heart lesion or not was doubtful. Roentgenograms showed the cardiac shadow slightly enlarged to the left side, consistent with the enlargement of the left ventricle. Cardiac dilatation or hypertrophy owing to congenital heart disease was considered possible. The head was small. Hearing was normal. The mental development was retarded. She could not feed herself well, could not talk plainly and could understand only simple sentences.

CASE 13.—*Deafness, congenital cataract, mental retardation, questionable congenital heart disease and a left sixth digit in a child whose mother was exposed to rubella at the end of the second month of pregnancy.*

J. L. C., a Negro boy, was born at term on March 15, 1943. Delivery was spontaneous and uncomplicated following an eight hour labor. The weight at birth was 9 pounds 10 ounces (4,365.8 Gm.). When the child was less than 6 months old, the parents were told by their physician that the child had a cataract in the right eye. As he grew older, the parents also discovered that the child was deaf and could make sounds but could not form words. When referred to our clinic at 4 years of age, the child could say only a few simple words such as "mama" and "dada."

The father, 25 years of age at the time of the child's birth, had been treated for traumatic cataract of the left eye when 21 years old. (This history of trauma was verified at the hospital where the father was treated.) A sister, niece and nephew of the father had each had a sixth finger on one hand. No other congenital anomalies had been noted in 23 members of his family. The mother, 18 years of age in 1943, was normal and healthy. No history of deafness, congenital heart disease or cataract was known in 27 members of her family. The mother's first and only pregnancy began in June 1942. In late August 1942, the mother had been exposed repeatedly to rubella through a child living in the same apartment house who had the disease. The mother had no symptoms of illness at that time or at any time during the nine months of pregnancy which culminated in the birth of J. L. D.

Physical examination of the child at 4 years of age revealed the following findings: A cataract of the right eye was noted. There was no blinking reflex on auditory stimuli. Both ears were irrigated with ice water. Caloric stimulation did not produce any reaction on either side (Dr. K. Tschiassny). No definite diagnosis of heart disease could be made. However, a soft systolic murmur was present at the apex and a roentgenogram disclosed the heart to be 8.8 cm. in a chest of 16.2 cm. On the left hand the stub of a sixth finger remained. The mental development of the child was felt to be subnormal, although psychometric testing could not be carried out.

CASE 14.—*Congenital unilateral cataract and microphthalmia, congenital heart disease and mental retardation (and deafness) in a child whose mother had no knowledge of illness during pregnancy.*

S. L. K., a white girl, was born at term on Jan. 15, 1942. The weight at birth was 4 pounds 1 ounce (1,842.7 Gm.). The newborn infant remained in the hospital for two months because of poor gain in weight. During that time the mother was told that the child had a congenital cataract of the right eye. In the next year and a half the child had repeated aural infections. During one of these attacks the mother learned that the child also had congenital heart disease. She was brought to our clinic in July 1945 for evaluation of the "heart trouble."

The father was 22 and the mother 20 years of age at the time of the birth of their only child. A pedigree of their families was prepared, including 28 members. No member charted had been known to have cataracts or congenital heart disease. The parents themselves could not recall having had any serious illnesses. The date of conception was thought to be April 19, 1941. The only complication during the pregnancy of two hundred and seventy-one days was moderate swelling of hands and feet from the third throughout the ninth month. The mother stated emphatically that no febrile illness or rash had occurred during the pregnancy.

Physical examination in July 1945 showed a 3½ year old child with a weight of 20 pounds (9.1 Kg.) and a height of 32½ inches (82.5 cm.). Microphthalmia and congenital cataract of the right eye were present. Examination of the heart disclosed enlargement to both the left and the right on percussion. A thrill was present to the left of the sternum in the third and four interspaces. A blowing systolic murmur, loudest at the aforementioned point, was transmitted over the whole precordium. Roentgenograms showed a heart of 9 cm. in a chest of 14 cm. Examination of the ears showed scarring of the tympanic membranes. Deafness, of undetermined origin, was stated to be present by several examiners, but the extent could not be evaluated because of lack of cooperation. Results of psychometric testing graded the child as "borderline defective," although she was rated "dull normal" in some phases of the testing.

CASE 15.—*Congenital heart disease, congenital cataract of the left eye, ptosis of the left eyelid and paresis of the right supranuclear seventh nerve in a child whose mother had a "common cold" at the beginning of pregnancy.*

C. T., a Negro girl, was born at term on Dec. 31, 1943. The delivery was spontaneous and precipitous. Her weight at birth was 5 pounds 6 ounces (2,438.1 Gm.). When this girl was 9 months of age, a physician told the mother that the child had a "bad heart" and a cataract of the left eye.

The father, aged 37 years at the time of the girl's birth, had had 3 children by a previous marriage, all living and well. There was no history of cataracts or heart disease in the father's family. The mother, aged 27 years, had no other children. No history of cataracts or heart disease could be found in her family. The mother gave a history of rubella in 1934. Her last menstrual period in 1943 began on March 25. Approximately seven to ten days later she had a "common cold," the only illness she had until the delivery of the girl, C. T., on December 31.

C. T. was seen in the Cincinnati General Hospital in October 1944, at the age of 9½ months. At that time her weight was 18½ pounds (8,401.5 Gm.). A cataract of the left eye, with ptosis of the left lid, was present. Paresis of the right supranuclear seventh cranial nerve was discovered. The heart rate varied from 140 to 160. In the third left interspace harsh systolic and diastolic murmurs were heard which were audible over the entire precordium. A roentgenogram disclosed a heart of globular configuration that was 6.5 cm. at its greatest width in a chest of 13 cm. The electrocardiogram showed a persistent tachycardia of 150, a low voltage in the T wave of lead III and a diphasic QRS complex in all three leads. The mental development of the child was stated to be normal.

COMMENT

In the pediatric department of the College of Medicine, University of Cincinnati, from 1944 to 1948 not more than 8 patients with congenital malformations were seen whose mothers gave a history of having had a rash during pregnancy. In 6 of these patients the rash was diagnosed as rubella, in 2 the mothers considered it to be "measles." There was no rubella epidemic in Cincinnati during these years and the conditions in 5 of the patients seen in the department were attributed to maternal rubella acquired elsewhere. None of the patients (except patients 2 and 3 who were included in this report but who were not seen in Cincinnati) showed both congenital cataract and congenital heart disease, the syndrome recognized and described at first by Gregg as a sequela of maternal rubella. None of the 8 children had congenital cataract; 4 had congenital heart disease; 7 were deaf; 2 were mentally retarded, and 2 had small heads. One child had a cleft in the posterior portion of the palate and no other congenital anomalies. The causal relationship between maternal rubella and congenital deafness was obscured in patient 7 by the fact that the mother had mumps in addition to rubella in early pregnancy, and in patients 6 and 9 by the report of the maternal rash as "measles."

During the same period 5 children were seen in the department who had congenital cataract and established or possible congenital heart

disease, but their mothers were not aware of having had rubella during pregnancy. After repeated questioning, 3 of these mothers remembered that they had been exposed to rubella in early pregnancy without noticing a rash subsequently; but 2 mothers knew of neither exposure to nor illness with rubella. Thus, in spite of the large number of abnormal children seen in the department, a relationship between maternal rubella and the syndrome of congenital cataract and congenital heart disease in the child could not have been recognized in our material without knowledge of Gregg's work and that of Swan and his co-workers. This statement is not meant to intimate doubt of Gregg's fundamental discovery, which we consider as well established; rather it represents an explanation and an apologia for pediatricians, who for many years missed the correlation between the maternal disease and the anomalies of the offspring. That the correlation is not new is borne out by cases 1 and 2 and 3 of our series in which the mothers had rubella as long ago as 1936 and 1930, respectively. Similar early cases were mentioned in a report of the Committee Appointed by the Director-General of Public Health of New South Wales (Australia) [2b]; but apparently it was impossible before 1941 to establish a causal relationship between the mother's disease and the child's anomalies. The admirable discovery of Gregg [1] and the work of Swan and his associates [6] were made possible by an epidemic of rubella which affected many adults. During the war, men and women who had not been exposed to rubella migrated from rural areas to crowded cities and army camps. An epidemic of rubella ensued in which many pregnant women were affected. Thus, Gregg was faced with a natural experiment which he recognized and interpreted correctly.

There are other reasons for the delayed recognition of the correlation of maternal rubella and malformations in the offspring. Rubella in the mother can produce a variety of clinical pictures in the child. It was mentioned previously that the children examined in the Children's Hospital, of Cincinnati, whose mothers gave a history of rubella in early pregnancy differed clinically from those described in Gregg's first publication. In our small series deafness was the most frequent congenital anomaly referable to maternal rubella. This is in agreement with later reports by Gregg and his associates [2b] and others [7] who

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6. Swan and others.[2a] Swan and Tostevin.[2c] Swan, C.: Study of Three Infants Dying from Congenital Defects Following Maternal Rubella in Early Stages of Pregnancy, J. Path. & Bact. **56**:289-295 (July) 1944.

7. Swan and Tostevin.[2c] Carruthers, D. G.: Congenital Deaf-Mutism as Sequela of Rubella-Like Maternal Infection During Pregnancy, M. J. Australia **1**:315-320 (March 31) 1945. Clayton-Jones, E.: Rubella as a Cause of Congenital Deafness in England, Lancet **1**:56-61 (Jan. 11) 1947. Altmann, F., and Dingmann, A.: Congenital Deafness and Cataract Following Rubella in the Mother, Arch. Otolaryng. **42**:51-52 (July) 1945.

found deaf-mutism in the majority of children affected by maternal rubella. Cataract and other ocular anomalies, such as buphthalmos, cloudy cornea at birth, coloboma and optic atrophy, are apparently rarer defects. Renal anomalies,[1] hypospadias,[2e] bicornate uterus, obliteration of the bile ducts,[2e] cleft palate, spina bifida occulta,[2c] talipes equinovarus [2b] and spastic diplegia also have been observed. Whether such anomalies occur oftener in children whose mothers had rubella during early pregnancy than in the general population cannot yet be stated. Large surveys, like those undertaken by Swan and his co-workers in Australia and by the American committee under the chairmanship of Dr. H. C. Miller, eventually will give information on this point. However, information available at present permits the conclusion that maternal rubella exercises a pleiotropic effect on the fetus. It may affect the eye, the brain, the ear and the heart. Blindness, deafness, a speech defect, spastic diplegia, athetosis, epilepsy, mental retardation and congenital heart disease may be manifestations of this postconceptional injury. The defects may occur singly or in a number of combinations. It was thought until recently that pleiotropic effects in prenatal pathologic lesions were always due to abnormal genetic action. Although it had been shown in animal experiments that accidental environmental agents can produce multiple and widespread pathologic effects in the embryo, the prenatal rubella syndrome shows that in man also syndromes of congenital anomalies may be due to postconceptional environmental causes and may not always be hereditary. While the existence of the pleiotropic effect of maternal rubella aided in elucidating this important principle of teratology, it delayed, in all probability, the recognition of maternal rubella as a cause of malformations, since the observers were confused by the variety of the disease pictures.

Swan and his co-workers suggesed [2c] that the type of congenital defect was dependent on the stage of pregnancy at which the mother acquired rubella. The first 9 children reported here whose mothers gave a history of rubella during pregnancy were deaf; the mothers dated their illness to various stages of pregnancy, from the third week to the fourth month. Congenital heart disease was found in patients 2, 3, 5, 6, 8 and 9. The mothers of the patients with cardiac disease dated their attack of rubella to the first or second month of pregnancy. Patients 4 and 7 whose mothers' rubella occurred in the third and fourth months of pregnancy were free of cardiac anomalies; the heart of patient 1 was not affected although the mother had rubella in the sixth week of pregnancy. Patients 4, 6, 7, 8 and 9 were mentally normal; patients 1, 2, 3 and 5 appeared mentally deficient. The

mothers of the mentally deficient children dated their illness to the first six weeks of pregnancy; the mothers of the mentally normal children had been ill in the second, third and fourth months of pregnancy. It appeared, therefore, that in this small series the eye, the heart and the brain were affected by rubella in the first two months of gestation, while the ear proved susceptible throughout the first four months.

Patient 10 was entirely normal except for a cleft of the soft palate. The mother had had rubella in the fourth week of pregnancy. The diagnosis of the maternal disease appeared well established, since it was made by a physician and the attack occurred during an epidemic. The family history was negative for cleft lip and palate. A similar case was recorded by Swan and Tostevin [2c] who observed a child with cleft of the soft palate whose mother had rubella (and possibly mumps also) in the first month of pregnancy. With our present knowledge of the teratogenic effect of maternal rubella, we can suspect a causal connection between the disease of the mother and the cleft palate of these children. Before the Australian epidemic, however, the association between the rubella of the mother and this malformation of the child would have been considered fortuitous. Cleft palate may be due to a variety of etiologic factors. It is genetically determined in many cases in man and in animals; it has been produced in animal experiments by such different environmental factors as riboflavin deprivation or exposure of the mother to roentgen rays. Other congenital anomalies, such as cataract, deafness, mental retardation and spastic diplegia, are equally unspecific manifestations of various prenatal disorders.

The fact that the same abnormality may be induced in embryos by a great number of different noxa [8] also contributed to the delayed recognition of the causal relationship between maternal rubella and congenital anomalies of the child. It is true that combinations of various congenital malformations (syndromes) are probably more specific expressions of a noxious agent than single defects. Thus, one may expect to obtain a history of maternal rubella during early pregnancy in many cases of congenital cataract and acyanotic heart disease. However, our patients 14 and 15 demonstrate that the typical syndrome may occur in mothers who to their knowledge were neither exposed to nor suffering from rubella or any other disease during

8. Stockard, C. R.: Development Rate and Structural Expression: An Experimental Study of Twins, "Double Monsters" and Single Deformities, and the Interaction Among Embryonic Organs During Their Origin and Development, Am. J. Anat. **28**:115 (Jan.) 1921.

pregnancy. Similar cases have been described by others.[9] Whether such unexplained cases are caused by "silent" rubella or not remains to be seen. It is not impossible for a woman to be exposed to rubella in early pregnancy without being aware of exposure and without showing signs of the disease. Theoretically, however, the same developmental errors could be caused by a different injurious agent.

The mothers of our patients 11, 12 and 13 were exposed to rubella during early pregnancy without having a noticeable rash. None of these mothers gave a definite history of having rubella in the past. It is likely, therefore, that they had the disease in a subclinical form. The mother of patient 12 actually reported a mild disease of the upper respiratory tract, sore throat and pains in the neck in the second month of pregnancy. An alternative explanation might be that the virus is transmitted to the embryo through the placenta of a mother who is immune to the disease. In a case of Swan and his co-workers,[9d] the mother of a child with cataracts, heart disease and microcephalia not only was well throughout pregnancy but also gave a history of having had rubella four years before the pregnancy in question. Such statements are not convincing as long as the diagnosis of rubella is based on clinical impression only, without objective proof of the presence of the virus of rubella or of antibodies produced by the disease. It is certain, in any case, that the majority of mothers who had rubella before pregnancy did not transmit a virulent rubella virus to the embryo when again exposed to the disease during pregnancy.

SUMMARY

In a five year period (1944 to 1948) only 8 children were seen in the Pediatric Department of the College of Medicine of the University of Cincinnati whose congenital anomalies could be attributed to rubella in the mother in the first trimester of pregnancy. Deafness was the most frequent defect observed in these children. Five of the 8 children, though born at term, weighed less than 6 pounds (2,721.6 Gm.) at birth. None of the patients presented the syndrome of congenital cataract and heart disease first recognized by Gregg as the combination of defects which follows maternal rubella in early pregnancy. However, the history of a pair of nonidentical twins with congenital cataract,

9. (*a*) Swan and others.[2a] (*b*) Goar, E. L., and Potts, C. R.: Relationship of Rubella in the Mother to Congenital Cataracts in the Child, Am. J. Ophth. **29**:566-569 (May) 1946. (*c*) Hopkins, L. A.: Congenital Deafness and Other Defects Following German Measles in the Mother, Am. J. Dis. Child. **72**:377-381 (Oct.) 1946. (*d*) Swan, C.; Tostevin, A. L.; Mayo, H., and Black, G. H. B.: Further Observations on Congenital Defects in Infants Following Infectious Diseases During Pregnancy, with Special Reference to Rubella, M. J. Australia **1**:409-413 (May 6) 1944.

heart disease and other defects is included in our report, although these patients were not seen in this pediatric department. These cases are important because they prove that rubella was teratogenic before the Australian epidemic. Another patient included in this report had congenital deafness and anomalies of the central nervous system attributable to maternal rubella in 1936. It is not necessary, therefore, to assume a change of the virulence of the rubella virus in 1940 in Australia.

An attempt is made to explain the reason that the prenatal rubella syndrome was not discovered before 1941. The fact that maternal rubella causes a great variety of anomalies which are not specific for this etiologic factor explains why an occasional observer could not draw the conclusions reached by Gregg who saw the results of an epidemic in which an unusual number of adults were affected. The occurrence of the "prenatal rubella syndrome" in children whose mothers do not give a history of having had rubella in early pregnancy contributes to the confusion of the occasional observer. The discovery of rubella as a cause of congenital anomalies was made possible through the correct interpretation of a natural experiment by a mind which was "prepared for it."

Elland and Bethesda Avenues.

FIBROSIS OF THE PANCREAS IN INFANTS AND CHILDREN

A Statistical Study of Clinical and Hereditary Features

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MINNEAPOLIS

THE CLINICAL syndrome fibrosis of the pancreas has received considerable attention in the medical literature of the world during the past ten years—so much so that the appearance of a patient with this disease is no longer regarded as unusual. Reports on the pathology, symptomatology, pathogenesis and etiology of the syndrome have appeared, and yet any critical appraisal of these publications makes it obvious that the complete picture is unknown. A review of the literature on the subject has recently appeared.[1]

The purpose of this report is to present a statistical analysis of the data which have been obtained from a study of 134 patients with fibrosis of the pancreas who were seen at the Infants' and Children's Hospital in Boston during the past ten years. No attempt has been

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Dr. Jane Worcester, Assistant Professor of Biostatistics, and Miss Olive Lombard, Research Fellow in Maternal and Child Health, Harvard School of Public Health, assisted in the preparation of the statistical material.

A large portion of the observations and collections of laboratory data found in the records of older patients included in this series was accumulated by the house staff.

1. Wiglesworth, F. W.: Fibrocystic Disease of the Pancreas, Am. J. M. Sc. **212**:351-365, 1946. Other less recent reviews have appeared: Rauch, S.; Litvak, A., and Steiner, M.: Congenital, Familial Steatorrhea with Fibromatosis of the Pancreas and Bronchiectasis, J. Pediat. **14**:462-490, 1939. Wolman, I. J.: Cystic Fibrosis of the Pancreas, Am. J. M. Sc. **203**:900-906, 1942.

made to evaluate or describe the clinical types of the disease, its course or its pathology. There remain, however, a number of intriguing questions: What are the racial, familial and hereditary characteristics of the disease? Is there a seasonal incidence? When does the disease have its onset, at birth or when thereafter? When do the various features of the disease appear, and in what order? What are the implications of the various features as regards prognosis? What can be learned from the incidence and significance of the roentgenologic and laboratory findings in this disease? Such questions are the points to which this communication is directed.

CLINICAL MATERIAL

Included in this survey were both children who had fibrosis of the pancreas alone and those who had meconium ileus associated with fibrosis of the pancreas. The association of meconium ileus with a characteristic lesion in the pancreas [2] which is identical with the lesion in infants and children with fibrosis of the pancreas has been well established.[3] In our experience, 3 patients who were relieved of their intestinal obstruction due to meconium ileus and who survived five to eight months or more ultimately exhibited the type of pulmonary lesion [4] seen clinically and pathologically in children with fibrosis of the pancreas. Later, analysis of duodenal contents revealed no tryptic activity in these patients.

The two groups when combined gave a total of 134 children with this disease. The 38 patients with fibrosis of the pancreas described in the first report from the Children's Hospital [5] were not included, for two reasons. First, the patients had been hospitalized between 1929 and 1937, and their parents had moved and lost contact with the hospital. Second, the information included in their records frequently contained little of the type of material included in the laboratory studies of the later patients. It was thus felt that the data on these patients would contribute little to the general statistical analysis.

The group included under the heading "fibrosis of the pancreas" consisted of 105 children. The diagnosis was established by estimation of duodenal tryptic activity in 82 children; 23 children died either before the diagnosis could be made or without the diagnosis being suspected. In each of these children a characteristic pancreatic lesion [4a] was found post mortem.

Twenty-nine children came to the hospital with a complaint of intestinal obstruction soon after birth, leading to a diagnosis of meconium ileus. Twenty-eight of them were operated on, and the surgical diagnosis of meconium ileus was

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2. Landsteiner, K.: Darmverschluss durch eingediktes Meconium: Pankreatitis, Centralbl. f. allg. Path. u. path. Anat. **16**:903-907, 1905.

3. Farber, S.: The Relation of Pancreatic Achylia to Meconium Ileus, J. Pediat. **24**:387-392, 1944.

4. (*a*) Farber, S.: Pancreatic Function and Disease in Early Life: V. Pathologic Changes Associated with Pancreatic Insufficiency in Early Life, Arch. Path. **37**:238-250 (April) 1944. (*b*) Baggenstoss, A., and Kennedy, R.: Fibrocystic Disease of the Pancreas: Study of Fourteen Cases, Am. J. Clin. Path. **15**:64-70, 1945.

5. Blackfan, K., and May, C. D.: Inspissation of Secretion, Dilatation of the Ducts and Acini, Atrophy and Fibrosis of the Pancreas in Infants, J. Pediat. **13**:627-634, 1938.

confirmed by the surgeon. One child received pancreatin orally and by enema, and his obstruction was relieved without surgical intervention. In this patient subsequent duodenal intubation revealed the absence of trypsin, and a diagnosis of fibrosis of the pancreas was made.

Analysis with respect to race, sex, parentage and siblings was made for all 134 patients. The data on 26 children with meconium ileus who were followed less than two months were excluded from the more general analysis, which included such factors as physical findings on admission, history and laboratory findings. Three children with meconium ileus lived more than two months and so were grouped with the children for whom complete analyses were made. Thus, the data on 108 patients are available for general analysis. Since some children had two or three siblings with fibrosis of the pancreas who were seen at this hospital, the group of 134 represents only 118 families. A summary of the case material is presented in table 1.

TABLE 1.—*Case Material Representing Fibrosis of Pancreas*

		No.
Patients with fibrosis of pancreas and/or meconium ileus seen at Children's Hospital since June 1938, who form the nucleus of the present study		134
Patients with meconium ileus followed less than 2 mo.	26	
Children with fibrosis of pancreas, including 3 with meconium ileus, followed more than 2 mo.	108	
Living patients, including 2 who had meconium ileus	43	
Patients who died with fibrosis of pancreas, including 1 with meconium ileus followed more than 2 mo.	65	
Siblings of children seen at Children's Hospital who from history presumably had fibrosis of pancreas and/or meconium ileus		33
Total no. of children with fibrosis of the pancreas		167
Total no. of affected families	118	
Families with 2 children with fibrosis of pancreas seen at Children's Hospital	12	
Families with 3 children with fibrosis of the pancreas seen at Children's Hospital	2	
Well children in 118 affected families		198
Total children in 118 affected families, including patients at Children's Hospital and well siblings		365

Information concerning race, family history, and the like, was obtained by letter or by special interviews with parents in those instances in which the child was no longer alive. Corresponding information concerning the living patients was obtained at the time of clinic visits.[6] In the case of 29 children with whose parents no contact was established, only the information available from the hospital record or through correspondence with the family physician was included.

OBSERVATIONS

Fluctuations in Apparent Onset.—The patients were arranged according to the calendar year of apparent onset of the disease. The children with meconium ileus were grouped according to year of birth, and the children with fibrosis of the pancreas, according to the year

6. Dr. William Berenberg, Dr. Stewart Clifford and Dr. John Davies permitted us to include their patients in this analysis, and they assisted in obtaining much of the clinical information on these patients.

in which the first symptoms of disease appeared. For 68 of 105 children, this date coincided with the date of birth. In table 2 these findings are summarized. It is apparent that the year 1942 showed the highest incidence of the two forms of the disease when combined. There does not seem to be any relationship between incidence of the disease and the fluctuations in the number of admissions to the Children's Hospital. The incidence appears to be independent of any sharpening of clinical suspicion, since the increase in fibrosis of the pancreas was accompanied with an increase in meconium ileus. Furthermore, the next year (1943) showed the second lowest incidence of the disease. In 1944 the incidence of fibrosis of the pancreas was the highest but there was only 1 case of meconium ileus.

One hypothesis of the origin of the disease suggests that it is an infection.[7] If this were so, the incidence of the disease might follow

TABLE 2.—*Year of Onset of Disease of 134 Children with Fibrosis of Pancreas and Meconium Ileus and Total Number of Admissions to Children's Hospital, Boston, During Same Years*

	1938	1939	1940	1941	1942	1943	1944	1945	1946	1947	Total	Average per Year
Fibrosis of pancreas.....	6	9	14	11	16	5	19	9	14	2	105	10.5
Meconium ileus.....	1	0	2	3	9	2	1	2	5	4	29	2.9
Total no. of cases.....	7	9	16	14	25	7	20	11	19	6	134	13.4
Total number of admissions to Children's Hospital..	..	6,312	6,600	6,365	6,496	6,746	6,789	6,866	..	..	...	....

a yearly fluctuation, as does that of certain other infections, being greater in epidemic years and waning in others. In view of evidence to be presented later, it is more likely that the fluctuations are purely random. The limits of the random fluctuations which may be expected are measured by the standard deviation. It can be shown that the standard deviation for the data in table 2 is equal to 6.5 cases. The average number of cases was 13.4 per year, and the limits between which purely random fluctuations may occur are set by this average plus and minus three times the standard deviation (13.4 ± 3 [6.5]). Accordingly, one may expect to find from none to 33 cases in any one year at the Children's Hospital. The fluctuations observed were all within these limits and are considered to be entirely random. There is nothing in this study which negates this conclusion.

Month of Birth.—The patients were arranged according to the month of birth in an attempt to see whether there was a significant monthly

7. Brody, H.: Concerning Etiology of Cystic Fibrosis of the Pancreas, New York State J. Med. **41**:1256-1259, 1941.

variation. Table 3 summarizes these findings. It is apparent that there was no significant monthly peak. Were the disorder an infectious one, affecting infants at or before birth, there might have appeared a significant variation in the monthly incidence of the disease.

Sex.—The distribution of 62 males and 72 females gives a sex ratio of 0.86. There is no statistically significant difference in the sex incidence.

Allergy.—Approximately 30 per cent of the families from whom adequate information was available gave a history of allergic diseases.

Race.—It is unlikely that much information would be obtained from a racial analysis, as practically all the patients were Caucasians. Among the small proportion of Negro patients at the Children's Hospital no case of fibrosis of the pancreas was found. Among the Caucasian groups there was only one Jewish family in which a case occurred, the other 117 families being non-Jewish. Our general impression is that the population of the Children's Hospital is about 10 per cent Jewish.

TABLE 3.—*Month of Birth of Children with Fibrosis of Pancreas and Children with Meconium Ileus*

	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Number of children...	19	7	10	11	12	11	15	12	6	12	13	6

If the impression is correct, one should expect more Jewish patients with this disease. Further study should be made to determine whether the occurrence of the disease in Jewish families is disproportionately small.

An attempt was made to distinguish between families of "English" and those of "Irish" derivation. Of 112 children of "English" descent, 52 (or 46 per cent) had the disease, and of 170 "Irish" children, 78 (or 46 per cent) had the disease. In the 365 children making up the whole population of all national derivations, 167 (or 46 per cent) had the disease. There were no differences between these last groups.

Relation of Total, Well and Affected Children in Different Family Groups.—When possible, parents were questioned concerning the total number of siblings in the family and the birth order of the affected children. Viable children who died soon after birth were included. Miscarriages and stillbirths were not included. A history of other children in the family who died of a disease similar to fibrosis of the pancreas or meconium ileus was elicited in certain cases. The criterion for accepting a case as one of fibrosis of the pancreas included the following points: failure to gain well soon after birth, chronic

disease of the respiratory tract, a good appetite, stool disturbances and, in several instances, autopsy observations at an outside hospital. The history of intestinal obstruction at birth with which the child lived at least four or five days was accepted as indicative of meconium ileus. It was found that there were 33 children never seen at the Children's Hospital who had a history sufficiently suggestive of this syndrome to be included in the present group. There were thus 167 affected children of the total 365 siblings.

In those instances in which no information was available concerning the total number of siblings, it was assumed that the patient was an only child. This was done with 3 patients. When no information was obtained concerning siblings with fibrosis of the pancreas, it was

TABLE 4.—*Correlation of Birth Order and Rate of Occurrence of Fibrosis of Pancreas*

Birth Order	Cases of Fibrosis of Pancreas	Number of Well Children	Total No. of Children	Attack Rate, Per Cent
1	45	73	118	38.14
2	49	49	98	50.00
3	36	35	71	50.70
4	16	18	34	47.06
5	6	12	18	
6	4	5	9	
7	5	3	8	43.18
8	0	4	4	
9	3	0	3	
10	1	1	2	
Totals	167*	200	365	45.75

* This total includes 2 sick children of unknown birth order. Since birth order of these 2 children with fibrosis of the pancreas is unknown, 2 extra children were included in the well column. This error is unavoidable, but probably insignificant.

$$50.70 - 38.14 = 12.56 \pm \sigma\Delta = 12.56 \pm 7.48$$

Since the difference between the two extreme rates is less than twice the standard deviation of the difference, there is no significant statistical difference between the rates.

assumed that the patient was the only child. This situation occurred in 4 cases.

It is important to ascertain whether parents are doomed to have the disease appear in consecutive children once a child with fibrosis of the pancreas is born in the family. That the disease strikes in a desultory way, skipping two, three or more children and then affecting one, became apparent. Findings concerning numbers of well and of affected children and their birth order are summarized in table 4 and shown graphically in chart 1. It is clear that there is no correlation between the birth order of the child and attacks of the disease, as the fluctuations in the rate of attack about the mean of 46 per cent are all small and of no significance. The lack of relation of birth order to occurrence of this disease indicates that any environmental factors peculiar to the age of the mother are of no significance.

Heredity.—A disease which is not very common in the population but which occurs several times in the same family may be suspected of having a hereditary background. In the case of this disease there is no transmission from parent to offspring, as no case of fibrosis of the pancreas in an adult is known. Children with the disease have always been born to normal parents and have themselves died before maturity. Consequently, the heredity cannot be that of a simple mendelian domi-

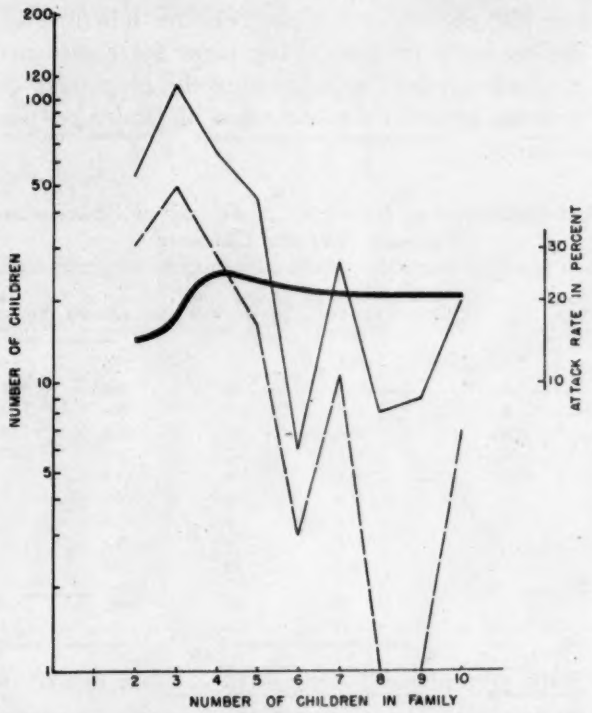

Chart 1.—Relation of number of children in the family to number of children with fibrosis of the pancreas. The abscissa shows the number of children in any given family group; the ordinate, the number of children in family groups of any given size. The light continuous line on the graph indicates the total number of children in families of any given size; the broken line, the number of children with fibrosis of the pancreas in families of any given size; the heavy continuous line, the rate of attack corrected for index case at any given family size. The light continuous line and the broken line are equidistant with more or less regularity. The rate of attack as drawn is not a straight line. However, statistically, this line could well be straight. If it were straight, then the light continuous and the broken line on the graph would be equidistant at all points.

The total number of children in families of the various sizes (light continuous line) is 365; the total number of children with fibrosis of the pancreas (broken line), 167; the rate of attack, corrected for index case (heavy continuous line), 19.8 per cent.

nant character. That as many girls as boys are affected by the disease excludes simple complete sex linkage, such as that shown by a character

like hemophilia. One may look, then, for evidence of inheritance as a single mendelian recessive. It should be apparent that in any family in which neither the parents nor the children are affected some one or more of them may carry the recessive character, but that they will never be suspected of doing so. Only those families in which at least one child is diseased will come to the attention of the investigator. Consideration of this observation led Macklin [8] to devise what may be called the "percentage affected method" for determining whether characters behaving like fibrosis of the pancreas are inherited as a single recessive. The reader is referred to her paper for a demonstration of the general principle involved in calculating the percentage of affected (diseased) children expected for each size of family on the basis of recessive inheritance.

TABLE 5.—*Demonstration of Inheritance of Fibrosis of Pancreas as Single Mendelian Recessive Character*

No. of Children in Family	Percentage Affected Expected	Total Children (Well and Sick)	No. Affected Expected	No. Affected Observed
1	100.0	20	20.0	20
2	57.1	54	30.4	31
3	43.2	111	48.0	49
4	36.5	64	23.4	28
5	32.8	45	14.7	16
6	30.4	6	1.8	3
7	28.8	28	8.1	11
8	27.7	8	2.2	1
9	27.0	9	2.4	1
10	26.5	20	5.3	7
		365	156.3	167

In table 5 the percentage of children expected to exhibit the disease is given in column 2. The only one child families to appear at the hospital will be those in which the child has the disease. Therefore 100 per cent of the children in the one child families are expected to have the disease. For two child families, either one or both children will have the disease, and of all the children in two child families, 57.1 per cent are expected to have the disease. As the family size increases, expectation for diseased children become closer to the classic 25 per cent expected from parents both of whom carry the gene for the disease but do not have it themselves.

Table 5 is an excellent demonstration of the inheritance of fibrosis of the pancreas due to a single recessive gene. In the fourth

8. Macklin, M. T.: Methods of Correcting Pedigree Data, J. Hered. **29**: 295-303, 1938.

column of the table are the figures for the number of children expected to have the disease. These figures are the products of values in column 2 multiplied by values in column 3. Finally, the expectations in column 4 may be compared with the observations at the Children's Hospital. No statistical treatment is necessary to show that there is good agreement between observation and expectation. There is a slight excess of sick children over the expectation, but this excess is well understood by the geneticist. In families of four or more children it is possible to have from one to many cases of the disease. The families

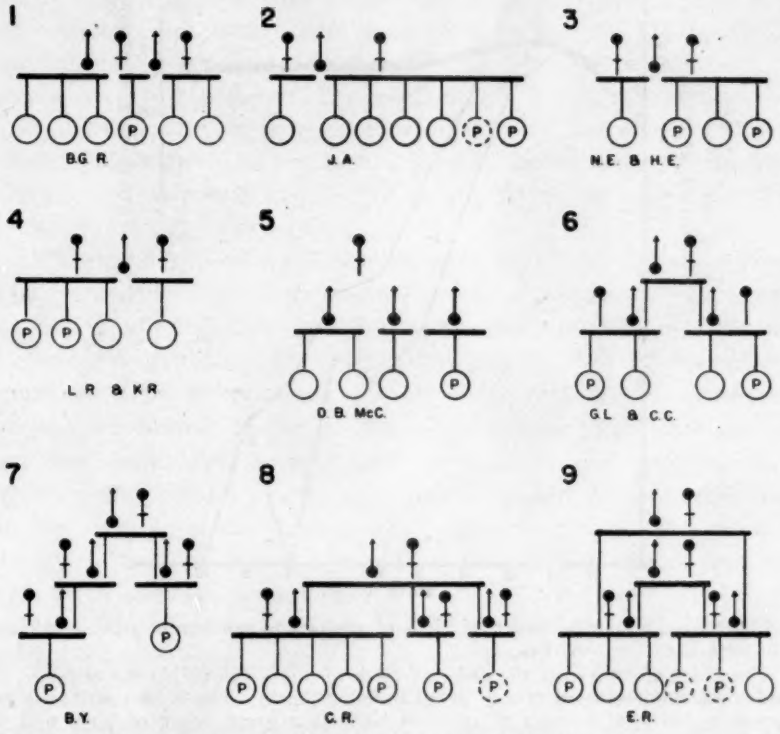

Chart 2.—Familial aspects of fibrosis of the pancreas.
A circle indicates a normal child; *P* in solid circle, a proved case of fibrosis of the pancreas; *P* in broken circle, a child with a history suggestive of fibrosis of the pancreas.

with the greatest number of sick children are the most likely to appear at the Hospital, whereas a large family in which only one child has the disease may not come to the attention of the Hospital. Consequently, large families bias the data so that a slight excess of observed over expected cases almost always occurs.

It is important for future research on fibrosis of the pancreas to reiterate that the disease behaves as a typical single recessive, fatal character. Future experiments should be designed with this essential fact in mind.

Andersen and Hodges [9] concluded from the study of their patients that fibrosis of the pancreas was due to a single mendelian recessive character. Howard,[10] considering certain aspects of the appearance of the

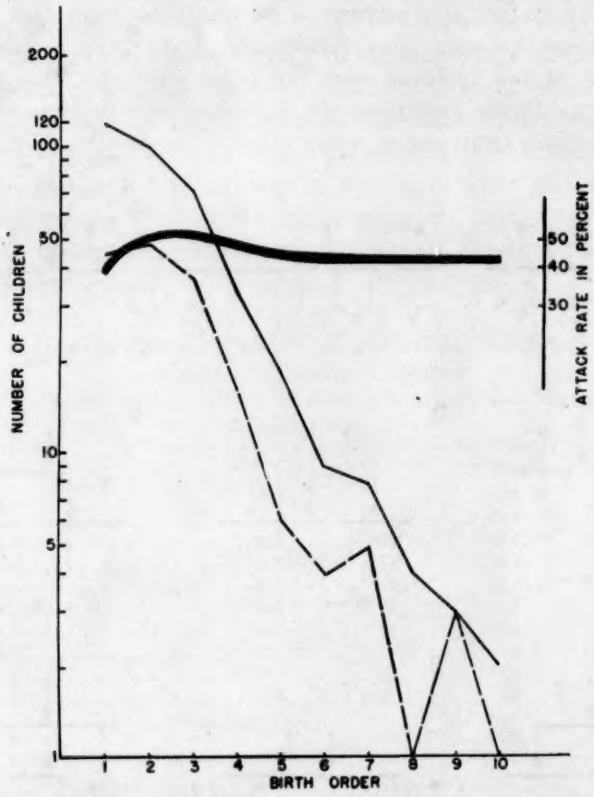

Chart 3.—Relation of order of birth of siblings to number of siblings affected with fibrosis of the pancreas.

The abscissa represents the order of birth of any given child; the ordinate, the number of children born at any given order of birth. The light continuous line represents the total number of children born at a given order of birth and the broken line the total children with fibrosis of the pancreas born at any given order of birth. The heavy continuous line represents the rate of attack obtained from table 16, not corrected for index case, at any given order of birth. Since the rate of attack statistically could be drawn as a straight line (table 16), the light continuous line and the broken lines could be drawn as equidistant, though discontinuous, lines. Since the sample is not large enough, true equidistance does not exist. It is probable that it would, were there sufficient numbers involved in the present survey.

The total number of children (light solid line) is 365; the number of sick children (broken line), 167, and the rate of attack, not corrected for index case (heavy solid line), 45.75 per cent.

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9. Andersen, D., and Hodges, R.: Celiac Syndrome: V. Genetics of Cystic Fibrosis of the Pancreas, with a Consideration of Etiology, Am. J. Dis. Child. **72**:62-80 (July) 1946.

10. Howard, P. J.: Familial Character of Fibrocystic Disease of the Pancreas, Am. J. Dis. Child. **68**:330-332 (Nov.) 1944.

disease in twins, came to a similar conclusion. Our material not only confirms their conclusion of recessive heredity but, in combination with the data of Andersen and Hodges, leaves no room for reasonable doubt that the disease results from a recessive gene which in the pure (homozygous) condition causes a defect of the pancreas.

Frequency of the Gene in the Population.—Now that the inheritance of fibrosis of the pancreas has been established, the question of how rare the gene may be becomes of interest. With rare genes it is found that there is a large amount of consanguinity in the parents. In this country something less than 1 per cent of all marriages are between first cousins. But with a rare gene, such as the one for xeroderma pigmentosum, it has been found that in 26 per cent of the cases the parents were first cousins. The general rule is that the incidence of cousin marriages among parents of children with a rare recessive disease becomes progressively higher as the trait itself becomes more infrequent. (See any text on human genetics for further discussion of this principle, which is known as Lenz's rule.)

Of the 118 families for which we have data, only 1 was reported to be consanguineous. This was the result of cousin marriage which produced 1 affected child and 3 normal children. The rate of consanguinity is therefore not distinguishable from that in the general population. This indicates one or both of two probabilities: either that the gene for fibrosis of the pancreas is not exceedingly rare or that there was more consanguinity than appeared in our records. Both conditions are probably true to some extent. Investigation farther back into the ancestry of the patients would undoubtedly reveal a common ancestry, of a more distant degree than that of first cousins, but one which was genetically important.

The first point, that the gene is not exceedingly rare, should be considered now. From table 2, it is clear that in approximately 12 of every 6,500 admissions to the Children's Hospital the children had fibrosis of the pancreas. The rest of the patients were not all the victims of hereditary disease, by any means, but many had broken limbs and the legion of calamities which children encounter. Furthermore, the 6,500 children were of all ages. An estimate of the percentage of cases of fibrosis of the pancreas in the population of the region is not a pure guess, but is guesswork with a certain amount of sense behind it. One can set extremely broad limits and know that the correct answer lies at an unknown point between them.

As a first step, we know, as will be shown in a later section of this paper, that this disease practically always manifests itself before the infant is 12 months old, and all patients in this study had shown the

first symptom of that disease before the age of 16 months. Consequently, we are interested only in the size of the population of infants of about 1 year or less who would be possible candidates for admission to the Children's Hospital in Boston if they were sick. It is quite probable that there are at least 1,200 infants of 1 year or less in age each year who might become candidates for admission to the Children's Hospital in Boston, but it is unlikely that there are more than 120,000 such young infants who would be likely to patronize this particular hospital. Thus, with 12 cases per year, the rate lies somewhere between 1 case per hundred and 1 case per 10,000. While this estimate is extremely rough, the limits should be broad enough to include the true rate. Obviously, a rate of 1 case per hundred children (1 per cent) is too high, but it is equally obvious that the rate could not be lower than 1 in 10,000 (0.0001 per cent). The true value must be somewhere between these two rates. Quite independently of our data on consanguinity, we have established the point that the gene for fibrosis of the pancreas is not particularly rare.

Another step may be taken which yields similarly inexact answers but gives valuable direction to our thinking. In a random breeding population there is a constant relationship between the number of persons exhibiting a recessive gene in the pure (homozygous) condition and those who carry the recessive gene in the concealed (heterozygous) condition. This relationship is indicated by the formula $p^2 + 2pq + q^2 = 1$. In this formula p^2 is usually taken as the rate or proportion of persons showing the disease, which in our case would be the infants with fibrosis of the pancreas. For the high rate estimate, then $p^2 = 0.01$, $p = 0.10$ and $q = 0.90$, while the low rate has $p^2 = 0.0001$, $p = 0.01$ and $q = 0.99$. The proportion of the general population which should carry the gene for fibrosis of the pancreas but would not have the disease themselves is equal to $2pq$ in the formula. The value for q^2 is equal to the proportion of persons in the population who neither have the disease nor carry the gene for it.

We are most interested in the value of $2pq$, as it tells us how many people in the general public carry the gene which in some way causes the disease of fibrosis of the pancreas. Using the preceding figures, $2pq$ equals 0.18 for the high rate estimate and $2pq$ equals 0.0198 for the low rate. To readers uninitiated in genetic lore, it may seem startling that somewhere between 2 and 18 persons of every hundred born in the Boston area carry the concealed gene for fibrosis of the pancreas. This is the case, however, to the extent that marriage of people in that region is at random. For all practical purposes, we are not particularly interested in the true value, which lies somewhere between 2 and 18 per hundred. It is the limits that are important.

Eugenic Implications.—The pediatrician specializing in the treatment of infants with this disease will undoubtedly be asked by the parents what the chances are that their next child might also have the disease, and whether or not it would be wise to have another child. The only correct answer is that the chances are precisely 1 out of 4 that the next child will have the disease and the parents must decide whether they wish to take a 1:4 chance.

History.—It has been found that infants with fibrosis of the pancreas tend to regain their birth weight rather slowly. Frequently they remain in what we have termed the "plateau period," of no appreciable

TABLE 6.—*Relation of Number of Children Showing Normal, Slow and Retarded Gain in Weight Before First Symptom to Number of Children Who Were Breast Fed* *

Feeding	Weight Gain			Total
	Normal	Slow	Retarded	
Breast fed 1-7 mo.....	8 (38%)	11 (52%)	2 (9%)	21
Not breast fed.....	32 (39%)	42 (51%)	7 (8%)	81

* When data were unknown, patients were omitted from totals.

TABLE 7.—*Type of Feeding and Vitamin A Supplement Before Hospitalization in Terms of Patients Now Living or Dead* *

Patients	Type of Feeding		Celiac Type of Diet Used		Adequate Vitamin A Before Respiratory Symptoms or Before 1 Month of Age	
	Ad lib	Restricted	Yes	No	Yes	No
Living.....	39 (91%)	4 (9%)	11 (26%)	32 (74%)	29 (83%)	6 (17%)
Dead.....	61 (94%)	4 (6%)	13 (20%)	52 (80%)	37 (79%)	10 (21%)

* When data were unknown, patients were omitted from totals.

gain in weight for from one to three months after birth.[11] It is of interest to determine the comparative effects of breast milk and ordinary cow's milk formulas during this period. The gain in weight was considered normal if the patient remained within the percentile into which he was born. It was considered slow if he dropped to a lower percentile and retarded if he actually failed to gain or lost weight. It can be seen by inspection of table 6 that there is no difference between the breast-fed group and the group fed cow's milk. It is possible that some food other than milk would prove more ideal during this "plateau period."

11. May, C. D., and Lowe, C. U.: Treatment of Fibrosis of the Pancreas in Infants and Children, Pediatrics **1**:159-173, 1948.

In table 7 the influence of the diet prior to hospitalization on the ultimate outcome of the patients is illustrated. All but 8 patients had received ad lib feeding to a greater or less degree up to the time of hospitalization. At some time before hospitalization 11 of the patients who lived and 13 who died received a "celiac" type of diet. It is apparent that the outcome was essentially uninfluenced by the type of diet given prior to hospitalization. This information has no bearing on the evaluation of dietary therapy subsequent to hospitalization. (This question has been considered extensively in another report, on the basis of experience with patients who had fibrosis of the pancreas in this clinic.[11])

Because deficiency of vitamin A has been proposed as a factor in one of the theories of pathogenesis of this disease,[12] parents were questioned carefully concerning vitamin supplements given prior to hospitalization. A summary of feeding and of vitamin A supplementation is presented in table 7. Since the same percentage of the living and of those who died

TABLE 8.—*Type of Gain in Weight Before and After Onset of First Symptom* *

	Weight Gain at Time of or Before Onset of First Symptom			Weight Gain After Onset of First Symptom		
Patients	Normal	Slow	Retarded	Normal	Slow	Retarded
Living.....	17 (40%)	19 (45%)	6 (15%)	6 (14%)	22 (51%)	15 (35%)
Dead.....	23 (38%)	34 (57%)	3 (5%)	6 (9%)	23 (35%)	36 (57%)

* When data were unknown, patients were omitted from totals.

were given inadequate vitamin A supplements prior to hospitalization, a deficiency in this vitamin would not seem to influence the prognosis or the course of the pulmonary process. Of the 10 patients who later died and who received no vitamin A supplement previous to hospitalization, autopsy was performed on 5; only 1 of them showed evidence of metaplasia suggestive of vitamin A deficiency.

Gain in Weight Prior to First Symptom.—Table 8 summarizes the gain in weight before and after appearance of the first symptoms in the living group and in the groups who later died. It is apparent that the proportion of the living who had a normal gain in weight prior to the first symptom is approximately equal to that of the similar group who later died. This is less true for the gain in weight after appearance of the first symptom. What is most striking is the large group of children who later died who either failed to gain or lost weight after their first symptom. Most commonly, when a patient has either

12. Andersen, D.: Cystic Fibrosis of the Pancreas, Vitamin A Deficiency and Bronchiectasis, J. Pediat. **15**:763-771, 1939.

respiratory or nutritional symptoms severe enough to require hospitalization, he has already commenced to lose weight.

If fibrosis of the pancreas begins at birth, and there is much evidence that it does in a majority of patients, then the normal gain in weight prior to hospitalization is even more striking. One of the less well appreciated features of this syndrome is the ability of some children to gain weight well in spite of their marked intestinal insufficiency.

TABLE 9.—*First Symptom of Patients Now Living or Dead*

Patients	Weight Loss or No Gain	Abnormal Stools	Cough	Total
Living	11 (26%)	20 (46%)	12 (28%)	43
Dead	21 (32%)	25 (39%)	19 (29%)	65
Total	32 (30%)	45 (42%)	31 (28%)	108

TABLE 10.—*Age at Onset of First Symptom*

	Age in Months at Onset of First Symptom											
	Birth	1	2-3	4-5	6-7	8-9	10-11	12-15	16-19	20-23	21 Over 24	Total
Patients now living	28	4	5	1	2	1	1	1	0	0	0 0	43
Patients now dead	40	5	9	3	3	2	1	2	0	0	0 0	65
Total	68	9	14	4	5	3	2	3	0	0	0 0	108

TABLE 11.—*Age at Appearance of First Symptom in Terms of First Symptom*

Age at Appearance of First Symptom	Weight Loss or No Gain	Abnormal Stools	Cough	Total
Birth	26 (24%)	35 (32%)	7 (6%)	68 (63%)
1-3 mo.	2 (2%)	5 (5%)	16 (15%)	23 (21%)
4-15 mo.	3 (3%)	6 (6%)	8 (7%)	17 (16%)
Total	31 (29%)	46 (43%)	31 (29%)	108 (100%)

First Symptom.—When possible, the age at onset of the patient's first symptom was determined. Questions were asked concerning loss of weight or failure to gain, symptoms referable to the respiratory tract and abnormal stools. As seen in table 9, 32 patients had loss of weight or failure to gain as their first symptom; 31 had respiratory symptoms, and 45 had gastrointestinal symptoms. When the living and those who died are arranged according to the first symptom, it is apparent that the two groups are approximately equal. In table 10 these children are grouped in terms of age of onset at first symptom, and it is evident

that well over half of them gave a history suggestive of the presence of the disease at birth. Eighty-three per cent had onset before the age of 3 months. The more careful the inquiry concerning the onset of symptoms, the more nearly the onset of the disease was found to date from birth. In table 11 there is an attempt to differentiate the initial symptoms in terms of age at onset. A significantly small group had complaints referable to the respiratory tract at birth. However, 56 per cent of the children had nutritional disturbances (those related to weight or stools) at birth. If all children with fibrosis of the pancreas have the disease at birth, the age of death should bear little relation to

TABLE 12.—*Age at Death in Terms of Age at Appearance of First Symptom*

Age at Death, in Months	Age in Months at Appearance of First Symptom												
	Birth	1	2-3	4-5	6-7	8-9	10-11	12-15	16-19	20-23	24	Over 24	Total
2-5	18	4	5	1	..	..	..	..	..	..	..	..	28
6-11	9	..	..	1	..	..	..	..	..	..	..	..	10
12 and over	13	1	4	1	3	2	1	2	..	..	..	..	27

TABLE 13.—*Age at Onset of Symptoms Referable to Respiratory Tract*

	Age in Months at Onset of Respiratory Symptoms												
	Birth	1	2-3	4-5	6-7	8-9	10-11	12-15	16-19	20-23	24	Over 24	Total
Patients now living	8	6	11	3	1	2	2	1	..	2	1	4	41*
Patients now dead	5	10	20	9	3	3	3	6	2	2	..	1	64†
Total no. of patients	13	16	31	12	4	5	5	7	2	4	1	5	105

* Two children are now alive, with no cough. They are not included in this total.
† One child is excluded, because date of onset of respiratory symptoms is unknown.

the age of onset of the first symptom. This seems to be borne out by table 12. Half the children who died at some age over 12 months had their symptoms from birth.

Symptoms Referable to the Respiratory Tract.—Seven of the 108 children did not manifest their respiratory symptoms until after the time of hospitalization. Two living patients have never had any respiratory complaints, although roentgenograms of their lungs are abnormal. It would thus seem that, regardless of the age at the time of hospitalization, symptoms of involvement of the respiratory tract usually exist by that time. If the living patients and the patients who died are arranged according to age of onset of symptoms referable to the respiratory tract, as in table 13, it is apparent that the majority of both groups had the onset of their respiratory symptoms between the

ages of 2 and 3 months. One might then amplify a statement made previously concerning symptoms of involvement of the respiratory tract and hospitalization: It is not the mere existence of these symptoms, but probably their severity, which leads to both hospitalization and death.

TABLE 14.—*Age at Death Versus Age at Onset of Symptoms Referable to Respiratory Tract**

Age at Death, in Months	Age in Months at Onset of Respiratory Symptoms												
	Birth	1	2-3	4-5	6-7	8-9	10-11	12-15	16-19	20-23	24	Over 24	Unknown
0-5	3	10	12	3	..	..	..	..	..	..	..	..	..
6-11	1	0	4	3	..	1	..	..	..	..	..	..	..
12+	1	0	4	3	3	2	3	6	2	2	0	1	1
Total	5	10	20	9	3	3	3	6	2	2	0	1	1

* When data were unknown, patients were omitted from totals.

TABLE 15.—*Age When Present Illness First Required Hospitalization*

	Age in Months When Present Illness First Required Hospitalization											
	1	2-3	4-5	6-7	8-9	10-11	12-15	16-19	20-23	24	Over 24	Total
Patients now living	6	10	4	1	5	3	3	3	1	3	4	43
	(20 [45%])			(12 [29%])				(11 [26%])				
Patients now dead	6	15	16	1	2	2	7	2	8	1	5	65
	(37 [57%])			(12 [18%])				(16 [25%])				
Total	12	25	20	2	7	5	10	5	9	4	9	108
	(57 [52%])			(24 [21%])				(31 [27%])				

TABLE 16.—*Age at Death Versus Age When Present Illness First Required Hospitalization*

Age at Death, in Months	Age in Months When Present Illness First Required Hospitalization											
	1	2-3	4-5	6-7	8-9	10-11	12-15	16-19	20-23	24	Over 24	Total
2-5	6	13	8	..	1	..	..	..	..	..	..	28
6-11	..	1	7	..	1	..	..	..	..	..	..	9
12 and over	..	1	1	1	0	2	7	2	8	1	4	27

In table 14 the children who died of this disease are arranged so that age at death is compared with age at onset of symptoms of involvement of the respiratory tract. It would seem, at least in the group who lived to be more than 12 months of age, that there is considerable variation in the interval between the onset of these symptoms and the patient's death. This probably is evidence not so much that the pulmonary lesion

did not always appear early but that its severity varied. Thus, the eventual prognosis is considerably related to the degree of pulmonary disease.

The majority of the patients who have survived for a relatively long time and of those who have died required hospitalization at approximately the same time, that is, at 6 months of age (table 15). In table 16, it appears that in the group who died, however, there was a tendency for longer survival when hospitalization was not required until after the age of 6 months. Some factor other than age of onset of symptoms referable to the respiratory tract determines the length of

TABLE 17.—*Relation of Appetite to Course of Fibrosis of Pancreas**

Patients	Appetite		
	Ravenous	Good	Poor
Now living	19 (44%)	22 (51%)	2 (5%)
Now dead	6 (9%)	42 (74%)	9 (17%)

* When data were unknown, patients were omitted from totals.

TABLE 18.—*Physical Findings at Time of First Hospitalization of Children Now Living or Dead**

Physical Findings	Patients			
	Living		Dead	
	Yes	No	Yes	No
Rales in chest	22 (51%)	21 (49%)	37 (59%)	26 (41%)
Weight below tenth percentile	34 (81%)	8 (19%)	51 (81%)	12 (19%)
Palpable liver	8 (19%)	34 (81%)	26 (42%)	36 (58%)
Wasting	26 (60%)	17 (40%)	49 (75%)	16 (25%)
Abdominal distention	20 (46%)	23 (54%)	33 (51%)	32 (49%)

* When data were unknown, patients were omitted from totals.

survival. We have called attention to the fact that one difference between the children who survived a short time and those who survived a longer time was the severer and more conspicuous pulmonary lesion in the former.

Stools.—From the parents of 15 of the children who died no history of abnormal stools prior to hospitalization could be obtained. This group of children was composed largely of those who either came to the hospital because of illness not related to fibrosis of the pancreas or were admitted and died almost immediately. It is possible that no effort was made at careful questioning concerning stool habits. When a good history was obtained, the majority of stools were described as foul and bulky.

Other Illness.—Two children died of causes other than fibrosis of the pancreas. In 1 instance it was meningitis; in the other it was volvulus of the small bowel. Three children had histories of grand mal seizures.

Appetite.—The remarkable appetites of patients with fibrosis of the pancreas has received some comment in the past. It would seem from table 17 that it has some slight prognostic usefulness. Apparently, almost half the living patients and only 9 per cent of those who died later had ravenous appetites. While many ill children retain their appetites, its absence indicates a poor prognosis.

Physical Findings.—The physical findings at the time of the initial hospitalization of the children with fibrosis of the pancreas have been

TABLE 19.—*Presence of Cyanosis and Clubbing at Some Time During Illness in Patients Now Living or Dead* *

Patients	Number of Patients with			
	Cyanosis	No Cyanosis	Clubbing	No Clubbing
Living	8 (19%)	34 (81%)	6 (14%)	37 (86%)
Dead	18 (29%)	44 (71%)	12 (20%)	47 (80%)

* When data were unknown, patients were omitted from totals.

TABLE 20.—*Relation of Age at Death to Presence of Clubbing and Cyanosis* *

Age at Death, in Months	Number of Children in Groups	Number of Children with Clubbing Reported	Number of Children with Cyanosis Reported
2-5	28	0 (0%)	11 (40%)
6 and over	36	11 (30%)	6 (17%)

* When data were unknown, patients were omitted from totals.

recorded in table 18. Abnormalities in the chest were not uniformly present in children with this disease. Only half the living children and half of those who died had rales in the chest on admission. A fairly characteristic finding was hyperresonance of the chest without other obvious abnormality on auscultation, percussion or inspection. This was present in 31 of the 108 patients. It thus seems that the degree of pulmonary involvement and respiratory distress in this particular series of children was not necessarily mirrored by the physical findings.

Half of both the children who died and the children who lived were below the tenth percentile by weight at the time of their initial admission. Frank wasting was present in three fourths of the children. It was impressive that the abdomen was noted to be protuberant or distended in only half the patients.

The liver was palpable in about one fifth of the children who survived and in about one third of those who later died. The reliability, however, of palpation in determining the size of the liver is particularly questionable in cases of this disease. Children with fibrosis of the pancreas frequently have such severe emphysema that the dome of the diaphragm is flattened, thus driving the liver downward. This possibly accounts for some of the occasions on which the liver was palpable.

TABLE 21.—*Pulmonary Change Shown in Roentgenograms at Time of First Hospitalization* *

Patients	Degree of Pulmonary Change at First Hospitalization			
	No Change	Mild	Moderate	Severe
Now living	3 (7%)	8 (19%)	13 (30%)	19 (44%)
Now dead	3 (5%)	14 (23%)	19 (31%)	25 (41%)

* Four of the patients who later died had no roentgenograms. Percentages are figured from a total of 61 patients.

TABLE 22.—*Bronchoscopic and Bronchographic Findings*

Patient	Age	Roentgenographic Abnormality of Chest *	Bronchoscopic Abnormalities	Bronchiectasis, Seen with Iodized Oil U. S. P.	Hypoplasia of Trachea	Suggestive Lining Deposit	Adequate Bronchogram
D.B.McC.	2½ yr.	3+	Minimal mucus	—	—	—	+
V.C.	2½ yr.	±	.....	—	—	—	+
C.D.	28 mo.	3+	Mucopus	+	—	—	Fair
E.G.	1 yr.	2+	Mucus; red mucosa	—	—	+	Fair
J.N.	2 yr.	2+	Minimal mucus	—	—	—	Fair
D.P.	5 yr.	3+	Tenacious mucopurulent material	..	..	..	..
C.R.	18 mo.	2+	.....	—	+	—	+
J.S.	6 yr.	3+	Thick mucus	Minimal fusiform dilatation; no saccular dilatation	—	—	+

* Abnormalities seen in roentgenograms of the chest were graded from ± to 4 +.

Clubbing of the fingers and cyanosis have been thought to be physical findings of serious portent. From table 19 it appears that a slightly larger percentage of the children who died than of the survivors had both cyanosis and clubbing. It is interesting that children with cyanosis may lose it; this happened in 7 of the 8 living children. Table 20 reveals that a higher percentage of the children who died between 2 and 5 months of age had cyanosis than did those who died after 6 months of age. This observation tends to substantiate the previous suggestion that the intensity of the pulmonary disease, not necessarily the age of onset of that symptom, is the factor which determines survival.

Congenital Deformity.—There was only 1 patient with a congenital anomaly, polydactyly.

Roentgenograms of the Lungs.—Almost all the children admitted, even those not suspected of having the disease, had roentgenograms of

TABLE 23.—*Blood Cell Count at First Hospitalization*

Age of Patient at Time of First Required Hospitalization, Months	Abnormal Red Blood Cell Count				Abnormal Hemoglobin Concentration			
	Yes	No	Unknown	Total	Yes	No	Unknown	Total
1-5.....	17 (30%)	37 (65%)	3	57	21 (37%)	32 (56%)	4	57
6 and over...	6 (12%)	43 (85%)	2	51	12 (23%)	36 (70%)	3	51
Total.....	23 (21%)	80 (74%)	5	108	33 (33%)	68 (63%)	7	108

TABLE 24.—*Erythrocyte Index of Children with Fibrosis of Pancreas*

Patient	Age	Red Cell Count, Millions	Hemoglobin, Gm./100 Cc.	Hemoglobin Concentration, % (Normal)	Mean Corpuscular Volume, (MCV), Cubic Microns* (Normal)	Mean Corpuscular Hemoglobin, Micromicrograms (Normal)	Mean Corpuscular Hemoglobin Concentration, (MCHC), %* (Normal)	Bone Marrow Aspiration
J.F.	8 yr.	5.11	14.4	44 (37)	86.1 (80)	28.1 (27)	32.8 (34)	.....
L.G.	3 yr.	4.67	13.6	41 (36)	87.7 (80)	29.1 (27)	33.1 (35)	.....
R.S.	6 yr.	4.08	12.35	38 (37)	93.1 (80)	30.2 (27)	32.5 (34)	.....
E.R.	3 yr.	4.21	11.9	39 (36)	95.0 (80)	28.2 (27)	30.5 (35)	.....
J.A.	10 mo.	4.87	10.9	36 (35.5)	74.0 (77)	22.3 (26)	30.3 (33)	.....
P.D.	13 mo.	4.01	10.9	40 (35)	100.0 (78)	27.0 (25)	27.0 (32)	.....
G.L.	5 mo.	4.67	9.3	32 (36)	68.0 (80)	29.0 (27)	19.9 (34)	.....
S.M.	8 mo.	4.06	12.6	39 (35.5)	96.1 (77)	32.3 (26)	31.0 (33)	.....
E.B.	2 yr.	4.88	10.75	39 (35.5)	77.0 (77)	22.0 (25)	27.5 (32)	.....
F.B.	4 yr.	4.05	12.5	38 (37)	93.0 (80)	30.0 (27)	32.0 (34)	Normal
R.C.	3 yr.	4.0	13.9	44 (36)	110.0 (80)	34.0 (27)	31.0 (34)	Normal
			Average	39.1 (36)	89.1 (79)	28.3 (26.5)	29.8 (33.6)	

* Δ MCV = 10.1 $\sigma\Delta = 3.7$ 10.1 ± 3.7
Δ MCHC = 3.85 $\sigma\Delta = 1.10$ 3.85 ± 1.10

The differences between values for patients and normal values seem to be statistically significant for the mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC). However, the errors inherent in determinations of this sort and the wide range of normal values (the median having been used for calculations below) make the clinical significance questionable.

Normal values were taken from Wintrobe, M. W.: Clinical Hematology, Lea & Febiger, Philadelphia, 1942.

their chests during hospitalization. The type of change seen in the lungs has been fully described in a report from this clinic.[13] The adjectives commonly used by the roentgenologist included "mild,"

13. Neuhauser, E. B. D.: Roentgen Changes Associated with Pancreatic Insufficiency in Early Life, Radiology **46**:319-328, 1946.

"moderate" and "severe" and serve as the basis for the arrangement in table 21. There is a remarkable similarity in the roentgenographic changes of the two groups. This, probably better than any other single fact, confirms the point that the process of the disease was identical in the surviving children and in the children who died, and that many factors determine the course of the pulmonary lesion.

As reports of the pathologic features of the pulmonary lesion describe bronchiectasis,[4a] it was deemed of interest to perform bronchoscopic and bronchographic studies on 8 children. The findings are summarized in table 22. Only 1 of the 8 children showed frank bronchiectasis, and 1 showed minimal, suggestive, early fusiform dilatation. The operators were impressed with the tenacious mucopurulent material in 2 of the patients, but this was not noted in the others. One patient showed what the roentgenologist described as hypoplasia of the tracheal tree. One might conclude from this study that at least among the children who survive bronchiectasis is not common. Perhaps it is one of the factors which leads to a fatal termination.

TABLE 25.—*Results of Oral Glucose Tolerance Test**

Patients	Low	High	Normal
Now living	3 (27%)	1 (11%)	7 (63%)
Now dead	9 (37%)	2 (9%)	13 (54%)

* When data were unknown, patients were omitted from totals.

Blood.—Patients with malnutrition, particularly children, and those with infection[14] are commonly anemic. In this connection, table 23 shows the interesting fact that the majority of these children had normal red cell counts and normal hemoglobin concentrations. Seventeen of the 23 children with abnormal red cell counts were less than 5 months of age, and 21 of the 33 children with abnormal hemoglobin concentrations were under 5 months of age. Thus, when either a low red cell count or a low hemoglobin concentration is present, it is more likely to be in the younger age group.

Erythrocyte indexes were obtained on 11 children. Table 24 summarizes these findings. All but 2 patients showed an increased mean corpuscular volume. The difference between the average value for these patients and that for normal children was statistically significant. The mean corpuscular hemoglobin tended to be normal. There was a tendency toward a low mean corpuscular hemoglobin concentration. Biopsies of the sternal marrow performed on 2 patients with macrocytosis revealed no cytologic abnormality.

14. Blackfan, K., and Diamond, L. K.: Atlas of the Blood in Children, New York, The Commonwealth Fund, 1944.

Glucose Tolerance Tests.—Oral glucose tolerance curves for children with "celiac disease" are regularly low.[15] In the case of fibrosis of the pancreas this is not true (table 25). The rise in the glucose tolerance curve was low for only 12 of 23 patients. For 3 patients there was a high rise in the glucose tolerance curve; this increase, however, was not unduly prolonged and was not characteristic of diabetes mellitus or accompanied with glycosuria.

TABLE 26.—*Relation of Roentgenographic Evidence of Disease of Bones To Serum Protein Concentration*

Roentgenographic Evidence of Disease of Bones	Serum Protein, Gm./100 Cc. 7	6	5	Not Determined	Total
Low bone age	2	..	2	9	13
None	1	4	1	9	15
Osteoporosis	7	3	2	6	18
Rickets	..	..	..	1	1
Scurvy	..	..	..	..	..
No roentgenogram	5	3	9	47	64
Totals	15	10	14	72	110*

* Two patients had evidence of two abnormalities each in roentgenograms.

TABLE 27.—*Relation of Roentgenographic Evidence of Disease of Bone to Calcium, Phosphorus and Phosphatase Concentration in the Serum*

Roentgenographic Evidence of Disease of Bones	Calcium, Mg./100 Cc. Low (Below 9)	Normal (9-12)	Unknown	Total	Phosphatase, Bodansky Units/100 Cc. Low (Below 5)	Normal (5-12)	Unknown	Total	Phosphorus, Mg./100 Cc. Low (Below 3)	Normal (3-4.5)	Unknown	Total
Low bone age	1	4	8	13	2	3	8	13	1	4	8	13
None	1	3	11	15	1	2	12	15	..	4	11	15
Osteoporosis	2	5	11	18	2	5	11	18	..	7	11	18
Rickets	..	..	1	1	..	..	1	1	..	..	1	1
Scurvy	..	..	..	..	..	..	..	..	..	..	..	..
No roentgenogram	1	4	59	64	1	4	59	64	..	4	60	64
Total	5	16	90	110*	6	14	91	110*	1	19	91	110*

* Two patients had evidence of two abnormalities each in roentgenograms.

Vitamin A Absorption Tests.—Vitamin A absorption tests were done on 72 patients. In every instance there was a barely perceptible rise in the vitamin A concentration of the plasma. A normal value for vitamin A absorption has not been observed for patients with fibrosis of the pancreas. In 1 case of another pancreatic disease encountered in

15. May, C. D., and McCreary, J.: The Glucose Tolerance Test in Celiac Disease, J. Pediat. **17**:143-154, 1940.

this clinic lipase was present but trypsin was absent. In this case the vitamin A absorption was normal. Low curves in the vitamin A absorption test occur in other disorders with impaired intestinal absorption of fat.[16]

Roentgenograms of the Bones, Blood Calcium, Phosphorus, Phosphatase and Serum Protein.—Roentgenograms of bones were taken on 44 patients. These were arranged according to the roentgenologist's interpretation. Tables 26 and 27 summarize the roentgenologic findings in relation to the calcium, phosphorus, phosphatase and protein concentrations of the blood. With these limited data, no single feature is apparent. It is interesting, however, that in a group of patients whose disease was accompanied with severe steatorrhea only 1 had rickets demonstrable roentgenographically. The commonest finding was osteoporosis, and the next commonest, retarded bone age. Serum protein determinations were made for 38 children. It is remarkable that in two thirds of these children, in spite of their debilitating disease, the serum protein levels were between 6 and 7 Gm. per hundred cubic centimeters.

Bacteriologic Observations.—Staphylococcus aureus was present in either the nose or the throat of 92 children and was not observed in 7 children. In the records of 9 patients there was no report of a culture being taken in this region. In patients in whom Staph. aureus was not found, only a single culture from the nose and throat was reported. Other pathogens, such as the pneumococcus, the streptococcus or the Hemophilus influenzae bacillus, were present in 59 patients. Apparently, the principal organism present in the respiratory tract of these children was Staph. aureus. Its absence was of no prognostic significance, since the 7 patients in whom it was not found in any examination died.

SUMMARY

A statistical analysis of the clinical data derived from 134 patients with fibrosis of the pancreas is presented.

In fibrosis of the pancreas and meconium ileus with fibrosis of the pancreas there was no significance in the fluctuation in frequency of the disease from month to month or from year to year. There was no significant difference in the sexual distribution of the disease. It is clear that the "English" and the "Irish" families are attacked with equal frequency by the disease, whereas a lower frequency of the disease in Jewish families is indicated. Further study should be made to determine whether the incidence of the disease in Jewish families is disproportionately small.

16. May, C. D., and McCreary, J.: The Absorption of Vitamin A in Celiac Disease, J. Pediat. **18**:200-209, 1941.

There was no observable relation of the birth order to occurrence of the disease, indicating that any environmental factor peculiar to the age of the mother is not of significance in the development of this disease.

It was possible to show by means of the Macklin "percentage affected method" that the hereditary background for fibrosis of the pancreas is a single mendelian recessive gene. This finding has been reported previously by other workers, but its importance to future research cannot be overemphasized. Two distinct lines of evidence indicate that the gene responsible for the character is not exceedingly rare. While it was not possible to calculate the exact frequency of patients with the disease from the data available, it was possible to show that the true frequency of affected persons in the general population up to about 1 year of age is somewhere between 1 in 100 and 1 in 10,000. Furthermore, between 2 and 18 persons out of every 100 in the general population carry the gene for fibrosis of the pancreas in the concealed heterozygous condition.

Breast feeding had no influence on early gain in weight. Those children who tended to survive longest had good gains in weight before appearance of their first symptom and fair gains in weight afterward. Stools of all the patients, when adequately described, were grossly abnormal. The commonest early symptom was abnormal stool, but, whether the first symptom was gastrointestinal, respiratory or nutritional, it seemed to bear little relation to the eventual outcome of the disease. In the majority of the children, both those who survived and those who died, the first symptom dated from birth. In most patients respiratory symptoms appeared by the fifth month, again in both the surviving patients and those who later died, and the majority of the children required hospitalization before 6 months of age. The commonest physical finding on admission was wasting or a weight which was below the tenth percentile. Some children, however, showed an impressive preservation of their nutritional state. Rales in the chest were not uniformly present, but in an appreciable number of children in whom they were absent the characteristic finding was noticeable hyperresonance. Cyanosis per se seemed to indicate a poor prognosis; but 8 children survived their cyanosis, and 7 of them are now free of it. Abdominal distention was present in only half the patients. Anemia was uncommon, and when it was present it was usually in infants below 6 months of age. There was surprising similarity in the roentgenograms of the lungs taken at the time of admission to the hospital of the children who are still living and of those who subsequently died, suggesting that at approximately corresponding stages in the development of their disease both groups required hos-

pitalization. Roentgenograms of the bones showed osteoporosis and were remarkable for the absence of rickets. This abnormality could not be clearly related to the calcium, phosphorus, phosphatase or protein concentrations of the serum. Staph. aureus was almost uniformly present in the nose and throat.

It may be reiterated that this study is a statistical analysis of certain clinical data, and that no attempt has been made to give a complete description of all the clinical manifestations, the derangements of metabolism or the course of the disease or to evaluate therapy. These aspects are the subjects of other communications.[17]

University of Minnesota (14).

17. May, C. D., and Lowe, C. U.: Fibrosis of the Pancreas in Infants and Children: An Illustrated Review of Certain Clinical Features with Special Emphasis on the Pulmonary and Cardiac Aspects, J. Pediat. **34**:663-687, 1949.

FATAL INTERSTITIAL AND MEDIASTINAL EMPHYSEMA

Following Accidental Needle Perforations of the Trachea During Jugular Venipuncture

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THE PHYSICIAN is often called on to puncture the veins of an infant, either to obtain a sample of blood for diagnostic purposes or to administer therapy. As a rule, the antecubital veins are too small for this procedure unless a vein is exposed through an incision in the skin. In order to avoid this difficulty larger calibered veins are employed, such as the longitudinal dural sinus beneath the fontanels or the femoral or the internal jugular veins; the last-mentioned vessel is usually the one of choice. This vein, however, lies in close lateral proximity to the trachea and tracheal perforation in connection with such venipuncture can readily occur. Such accidents have not been thus far recorded in the literature.

It is, therefore, my purpose in this paper to report 2 cases of accidental fatal perforation of the trachea in infants during venipuncture of the internal jugular vein and to discuss the mechanism of the production of the interstitial emphysema, pneumomediastinum, pneumopericardium and pneumothorax which can result from such an injury.

The term interstitial emphysema denotes that condition in which gas is present in the connective tissue of any part of the body.

Macklin and Macklin [1] used the term pulmonic interstitial emphysema, based on their anatomic studies which indicated that the emphysema has its origin in the lungs and that the other complications, namely, pneumomediastinum, interstitial emphysema and pneumothorax, are secondary.

REPORT OF CASES

CASE 1.—A full term, female Negro infant was delivered on Feb. 14, 1947, by cesarean section because of premature separation of the placenta. The infant appeared healthy, reacted normally and took her feedings well. When she was 7 days old, a puncture of the left internal jugular vein was performed to obtain blood for a Wassermann test. Following this procedure, there were rapid develop-

From the Office of the Chief Medical Examiner, City of New York.

1. Macklin, C. C., and Macklin, M. T.: Pulmonic Interstitial Emphysema and Its Sequelae: An Anatomical Interpretation, in Essays in Biology in Honor of Herbert M. Evans, London, Canada, University of Western Ontario Medical School, 1943, pp. 337-368.

ment of subcutaneous emphysema and gradual onset of dyspnea and listlessness. The clinical impression was that the apical pleura had been perforated. Attempts were made to remove air from the pleural cavities. Despite the administration of stimulants and blood transfusion, the respirations gradually decreased in frequency and the infant died two and one-half hours after the onset of symptoms. Because of the unexpected character of the death following venipuncture, the case was reported to the Office of the Chief Medical Examiner and an autopsy was performed.

Autopsy Observations.—The body was that of a 7 day old female Negro infant, somewhat underweight and undersized but otherwise normally formed; its scale weight was 2,165 Gm. and its length, 19 inches (48 cm.). Subcutaneous emphysema, involving the entire scalp, face, neck and upper part of the anterior wall of the chest was conspicuous. Several fresh needle puncture marks on the left side of the neck over the course of the internal jugular vein and multiple needle punctures on the anterior surface of the chest over the pleural cavities and precordium were observed. The diaphragm was at the level of the fourth right and fifth left interspaces. The abdominal viscera were normal. A pneumothorax test gave a positive reaction for both pleural cavities, a small amount of air under pressure escaping from each, more from the right than from the left. The lungs were observed to be collapsed, occupying the posterior half of the pleural cavities. The tissues of the superior and anterior mediastinum were distended with large various-sized emphysematous bullae. The areolar connective tissue at the base of the neck appeared foamy owing to the presence of extravasated air. Similarly, when the scalp was reflected, the areolar tissues between the scalp and the pericranium were seen to be infiltrated with air.

Careful examination of both pleural cavities did not disclose any needle puncture in the apical portions of the parietal pleura. The thymus was fleshy, pinkish gray and bilobed, lying normally in the superior mediastinum, with slender upward prolongations into the neck, and extending downward on the upper anterior portion of the pericardium. There was a small amount of freshly extravasated blood in the interstitial tissues of the left side of the neck along the great vessels. The tongue and the organs of the neck and thorax were removed *en masse;* the pharynx and esophagus appeared unobstructed. On opening the left internal jugular vein, needle puncture marks were seen in its midportion. Dissection of the trachea revealed a small transverse needle puncture in the upper part of the anterior wall just below the isthmus of the thyroid gland. This needle puncture was more conspicuous when the trachea was examined from within; it was 1 mm. in width, located exactly in the midline and filled with a small blood clot, and was the obvious source of the mediastinal and subcutaneous emphysema. No other tracheal punctures were observed. The lungs were about equal in size and completely airless and sank in water. The gas blebs in the areolar tissue of the anterior mediastinum were ruptured in handling. The heart was normal and contained a small amount of dark red fluid and soft clotted blood. The fossa ovalis was open anteriorly but the opening overlapped; the ductus arteriosus was not completely obliterated. The abdominal viscera were normal. There were no intracranial abnormalities. The ossification centers in the lower femoral and upper tibial epiphyses were indicative of a full term gestation.

The cause of death was subcutaneous and mediastinal emphysema, bilateral pneumothorax and pulmonary atelectasis, following needle puncture of the trachea during diagnostic puncture of the left internal jugular vein.

CASE 2.—A full term, white female infant was delivered spontaneously in the hospital. Although the infant was apparently normal, the mother was known to be syphilitic. An attempt was made, on the ninth day of the infant's life, to obtain blood for a serologic test from the right internal jugular vein, but since the puncture was not successful it was necessary to obtain the blood from the right femoral vein. An immediate swelling of the right side of the neck and of the wall of the chest was noticed; the clinical impression was that a traumatic perforation of the lung had taken place during the attempt to puncture the jugular vein. The infant died forty minutes after the venipuncture was attempted. The death was reported to the Office of the Chief Medical Examiner.

Autopsy Observations.—The body was that of a normally formed white female infant, 50 cm. long and weighing 2,830 Gm. The finger nails were cyanotic, and there was conspicuous subcutaneous emphysema, involving the scalp, face, neck and upper part of the trunk. The diaphragm was found at the level of the sixth rib on each side and appeared slightly depressed. The lungs were pinkish gray and aerated and did not exhibit any interstitial emphysema. The bronchi were not obstructed. The heart and pericardium were normal. The abdominal viscera were congested but otherwise normal. A needle puncture mark surrounded by a faint bluish area of ecchymosis was observed in the right side of the neck, situated 1.5 cm. posterior and 2.5 cm. below the level of the lower attachment of the right ear.

The organs of the neck were removed. Dissection then revealed that the track did not penetrate the jugular vein but that it passed posterior to it and punctured the right side of the trachea between the sixth and seventh tracheal rings. There was considerable emphysema in the areolar tissues of the neck, especially on the right side, in the paratracheal tissues and in the superior and posterior mediastinal areolar tissues, which were distended by blebs of gas. The needle puncture mark over the upper part of the femoral vein on the right thigh, from which blood had been successfully withdrawn, was also noted.

The cause of death was subcutaneous cervical and mediastinal emphysema, following needle puncture of the trachea during attempted diagnostic venipuncture of right internal jugular vein.

COMMENT

The cervical fascia is composed of a superficial and a deep, or pretracheal, layer with a loose areolar connective tissue in between which directly communicates with the loose connective tissue of the mediastinum. The anatomic pathways by which air may reach the mediastinum, the interstitium of the lungs or the pleural cavities are: (1) through a perforation of the apical parietal pleura; (2) by rupture of pulmonary alveoli, permitting extension of air through the interstitial connective tissue planes of the lung to the mediastinum with further extension into the pericardial sac (pneumopericardium), or by rupture of the mediastinal connective tissue into the pleural cavity (pneumothorax); (3) by rupture of the visceral pleura; (4) by escape and extension of air through an opening in the airway in the region of the neck, with extravasation into the areolar tissue between the superficial and deep layers of the cervical fascia, with extension into the mediastinum and by rupture of

the mediastinal pleura into the pleural cavity to produce a pneumothorax, and (5) by the entrance of air into the planes of cervical connective tissue, following exposure of these tissues during surgical procedures.

Hamman,[2] in 1937, reported 6 cases of spontaneous interstitial emphysema which developed during moderate or slight physical exertion, while the patient was shaving, getting out of a car or walking on the street, or during minimal or no exertion, while the patient was sitting in a train, in bed or in a chair. Trauma did not play a part in any of this author's cases.

Fisher and Macklin [3] reported a case in which pulmonary interstitial and mediastinal emphysema occurred in a 22 month old infant following the aspiration of peanut fragments. Smith and Bowser [4] reported 2 cases of pneumomediastinum in premature infants following spontaneous delivery. Fisher [5] described a fatal case of spontaneous pulmonic interstitial emphysema occurring in an infant five hours after delivery. There was atelectasis of the left lung and compensatory emphysema of the right lung.

Cases of spontaneous interstitial emphysema of the lungs have been reported in which the condition developed in a 27 year old laborer who was pushing a wheelbarrow [6]; in a 17 year old girl who was standing, dribbling a basketball [7]; in a person following a 100 mile (160.9 Km.) bicycle race, and in another person after a ½ mile (0.8 Km.) foot race [8]; in a person working in a laboratory with a Haldane apparatus,[9] and in a 39 year old woman fifteen minutes after a spontaneous delivery.[7] Nussbaum,[10] in a review of the literature, reported interstitial emphysema

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2. Hamman, L.: Spontaneous Interstitial Emphysema of the Lungs, Tr. A. Am. Physicians **52**:311-319, 1937.

3. Fisher, J. H., and Macklin, C. C.: Pulmonic Interstitial Emphysema and Mediastinal Emphysema, Am. J. Dis. Child. **60**:102-115 (July) 1940.

4. Smith, A. B., and Bowser, J. F.: Spontaneous Pneumomediastinum (Mediastinal Emphysema), with Reports of Two Cases in Infants, Radiology **38**:314-319 (March) 1942.

5. Fisher, J. H.: Spontaneous Pulmonic Interstitial and Mediastinal Emphysema in Infants, Canad. M. A. J. **44**:27-29 (Jan.) 1941.

6. Wolff, B. P.: Spontaneous Interstitial Emphysema of the Lungs: Report of an Additional Case, Ann. Int. Med. **13**:1250-1252 (Jan.) 1940.

7. McGuire, J., and Bean, W. B.: Spontaneous Interstitial Emphysema of the Lungs, Am. J. M. Sc. **197**:502-509 (April) 1939.

8. Scott, A. M.: The Significance of the Anginal Syndrome in Acute Spontaneous Pneumomediastinum, Lancet **1**:1327-1330 (June 5) 1937.

9. Morey, J. B., and Sosman, M. C.: Spontaneous Mediastinal Emphysema, with Report of a Case Associated with Spontaneous Pneumothorax, Radiology **32**:19-22 (Jan.) 1939.

10. Nussbaum, F. H.: Subcutaneous Emphysema Arising During Labour, Brit. M. J. **2**:1169 (Dec. 11) 1937.

during and after parturition. Gordon [11] had managed to collect 130 cases from the literature.

Berkley and Coffen,[12] in 1919, during an influenza epidemic in an army camp, were the first to demonstrate roentgenologically that the pulmonic air streaks seen on their films were the single cause for the air in the mediastinum. They also expressed the opinion that this mechanism explained the simultaneous appearance of pneumothorax and subcutaneous emphysema.

Barrie [13] reported 4 fatal cases of interstitial emphysema and mediastinal emphysema with pneumothorax. Three followed partial thyroidectomy, and the fourth occurred after tracheotomy for glottic edema. The air entered the tissues through the operative wound and then traveled into the mediastinum; the pneumothorax occurred after rupture of the emphysematous mediastinal tissues. Michels [14] reported 6 cases of pneumothorax and mediastinal emphysema following tracheotomy. Other cases following tracheotomy have been reported.[15] Interstitial emphysema has also been reported as the result of asthma [16] and whooping cough [17] and in diphtheria.[18]

In conditions in which there is vesicular emphysema, such as asthma, whooping cough, tuberculosis or chronic bronchitis, a sudden increase in pressure is sufficient to rupture the attenuated wall of the distended alveoli and allow the passage of air into the interstitial connective tissues of the lung.[19]

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11. Gordon, C. A.: Respiratory Emphysema in Labor with Two New Cases and a Review of One Hundred and Thirty Cases in the Literature, Am. J. Obst. & Gynec. **14**:633-646 (Nov.) 1927.

12. Berkley, H. K., and Coffen, T. H.: Generalized Interstitial Emphysema and Spontaneous Pneumothorax as Complications of Bronchopneumonia, J. A. M. A. **72**:535-539 (Feb. 22) 1919.

13. Barrie, H. J.: Interstitial Emphysema and Pneumothorax After Operations on the Neck, Lancet **1**:996-998 (June 1) 1940.

14. Michels, M. W.: Pneumonthorax and Mediastinal Emphysema Complicating Tracheotomy, Arch. Otolaryng. **29**:842-852 (May) 1939.

15. Goldberg, J. D.; Mitchell, N., and Angrist, A.: Mediastinal Emphysema and Pneumothorax Following Tracheotomy for Croup, Am. J. Surg. **56**:448-454 (May) 1942.

16. Rosenberg, L., and Rosenberg, J.: Spontaneous Emphysema Complicating Bronchial Asthma, Am. J. M. Sc. **195**:682-685 (May) 1938.

17. Beaumont, G. E.: Medicine: Essentials for Practitioners and Students, ed. 2, London, J. & A. Churchill, Ltd., 1934, p. 152.

18. Rolleston, J. D.: Diphtheria with Perforation of Larynx, Letters, Notes and Answers, Brit. M. J. **1**:120 (Jan. 23) 1943. Rolleston, J. D.: Non-Surgical Subcutaneous Emphysema in Laryngeal Diphtheria, Brit. J. Child. Dis. **25**:185-188 (July-Sept.) 1928.

19. Bryan, T. B. L.: Interstitial Emphysema, East African M. J. **22**:349-359 (Nov.) 1945.

Trauma, either accidental or during surgical treatment of the larynx, trachea, bronchial system or pulmonary alveoli may result in interstitial emphysema. Although the usual injury is a perforating wound of one of these structures, interstitial emphysema is a frequent accompaniment of contusion of the lung, and, indeed, subcutaneous emphysema in the neck may be the only sign in mild cases of pulmonary contusion [19]

MECHANISM OF PRODUCTION OF INTERSTITIAL EMPHYSEMA

Hamman [20] postulated that following rupture of a pulmonary alveolus air reaches the interstitial tissue spaces and travels along the connective tissue spaces in the lung to the perihilar region and then into the mediastinum. He considered that the air might also travel to the periphery of the lung, where it might form a bleb beneath the visceral pleura, and that the rupture of such a bleb would be the cause of any associated pneumothorax.

Macklin and Macklin,[1] by many anatomic studies, demonstrated that the pulmonic connective tissue is confluent and that, whether peribronchial, perivascular or perilobular, it extends directly through the root of the lung into the mediastinum and beyond. This loose connective tissue is easily separated by air which may gain entrance to it. They emphasized the fact that for air to break out of the alveolus through the thin alveolar base into the surrounding connective tissue sheath of the vascular network, one of two factors, or both together, was necessary. These were designated by him as leakage-favoring factors "A" and "B." "A" is that factor which operates when the alveolus becomes overdistended without a simultaneous and equivalent swelling of the blood vessel, initiating a downward pressure gradient between air and connective tissue and, in consequence, minute ruptures may be formed in the thin base of the alveolus through which air enters the connective tissue sheath. The "B" factor operates when the blood vessels shrink without an equivalent narrowing of the alveolar envelopes.

Macklin and Macklin were not of the opinion that lacerations of the mucosa of the upper airway, such as occur in tracheotomy in intratracheal anesthetization or from the introduction of an instrument into the trachea, are the sites of origin of the resultant interstitial emphysema. They stated their feeling, rather, that if all cases of pulmonary interstitial emphysema could be searched through to their origin, it would be found that atelectasis, by inducing compensatory alveolar emphysema, is the origin of many, if not most, of them. Air which has traveled to

20. Hamman.[2] Hamman, L.: Spontaneous Mediastinal Emphysema (Henry Sewall Lecture), Bull. Johns Hopkins Hosp. **64**:1-21 (Jan.) 1939.

the mediastinum from the vascular sheaths of pulmonary connective tissue tends to develop a pressure greater than that of the atmosphere. This air in the pulmonary connective tissue and mediastinum sets up an airblock which affects two vital functions, circulation and respiration. The airblock mechanism may cause death if the increased pressure of the mediastinal air is sufficient to compress the mediastinal contents. Auricular and ventricular filling may be hampered, the great vessels pressed on and the systemic venous return slowed and even halted. An increase of the pressure in the mediastinum is reflected back into the lung, and the aberrant air pressure there also rises. The increased air pressure in the mediastinum could result in extravasation of the air into the subcutaneous tissues of the neck or into the pleural cavities, with the formation of pneumothorax. If the pneumothorax develops on the affected side, it has a tendency to stop the primary leak in the lung. From the mediastinum, the airblock can extend to the opposite lung and further embarrass the respiratory system.

Although the mechanism demonstrated and described by Macklin and Macklin undoubtedly occurs in many cases, it does not appear to be the only method for the production of subcutaneous and mediastinal emphysema. The 2 cases of tracheal perforation reported herein suggested another mechanism for its production; namely, the passage of air into the loose connective tissue between the cervical fascia and its extension through existing anatomic planes of cleavage into the mediastinum, where the air, if it attains a great enough pressure, may rupture the mediastinum and extravasate into the pleural cavities.

Goldberg, Mitchell and Angrist[15] in their paper on mediastinal emphysema and pneumothorax following tracheotomy in cases of croup also were of the opinion that, in their cases, the air had dissected down the fascial planes of the neck into the mediastinum. In 1 of their cases, because of a technical difficulty, there was considerable delay after the fascial planes of the neck were exposed before the incision into the trachea could be made. During that interval, the aspiration of air was heard through the edges of the wound as the result of the forceful inspirations of the infant. Two hours after the operation, it was noted that the child was becoming increasingly more dyspneic. Results of physical examination suggested the presence of bilateral pneumothorax, which was confirmed by the roentgenogram. The authors pointed out that if mediastinal emphysema were due to rupture of an alveolus and escape of air along the pulmonary connective tissue pathways incident to the high negative pressures developed during obstructive breathing, the condition should be encountered more commonly before tracheotomy. Roentgenograms taken before tracheotomy in their cases failed to dis-

close any mediastinal emphysema or pneumothorax. To check the interpretation of their clinical data and postmortem observations further, they devised an experiment using 9 cadavers, ranging in age from a stillborn child of six months' gestation to a 1 year old infant, in each of which the body was opened and the contents of the mediastinum exposed entirely under water. The fascial planes of the neck were identified by sharp dissection, and air was injected under positive pressure through a 20 gage needle, inserted beneath the superficial and deep layers of the cervical fascia. They observed the dissection of the air down the fascial planes into the anterior mediastinum and the formation of large emphysematous belbs in the mediastinal tissues. After injection of 20 to 50 cc. of air under a pressure of 15 to 20 mm. of mercury, they observed that no more air would enter the mediastinum until the pressure was raised considerably. When a pressure of 40 mm. of mercury was reached, there was a rapid fall of the pressure to 0, coincident with the rupture of an emphysematous bleb into the pleural cavity, after which occurrence more air could be injected at much lower pressures. In another experiment the injection of air into the main bronchus under forced pressure resulted in inflation of the lung. Aberrant air could be seen in the subpleural connective tissue. If the pressure was further increased, rupture of the pleura occurred, usually through the hilus in the mediastinum. The results were similar to those of Macklin and Macklin.[1]

In the 2 cases of interstitial and mediastinal emphysema following tracheal puncture which are reported in this paper, the air reached the cervical interfascial connective tissue and mediastinum through the puncture wound in the trachea and was drawn into the tissues by the negative inspiratory intrathoracic pressure or forced through by the positive expiratory pressure.

The treatment of mediastinal and interstitial emphysema has been described by many authors. Essentially, it consists of procedures which attempt to overcome the air block that has developed in the mediastinum. Aspiration from the pleural cavity of air if pneumothorax has developed, or of air trapped in the mediastinum, has been attempted, and operations have been devised to enter the posterior mediastinum in order to free any trapped air.

Puncturing the neck with a needle to draw blood from the internal jugular vein is not without danger in that the close proximity of the trachea exposes that structure to a perforating injury which may be rapidly complicated by fatal interstitial and mediastinal emphysema. Diagnostic or therapeutic venipuncture in this location should be carried out with the greatest of care because of the danger involved.

SUMMARY

1. Two cases of fatal interstitial and mediastinal emphysema occurred following needle puncture of the trachea incident to jugular venipuncture.

2. Pulmonary interstitial emphysema, pneumomediastinum and pneumothorax and the mechanism of their production are discussed.

3. Following needle puncture of the trachea, air rapidly enters the fascial planes of the neck extravasating into the subcutaneous tissues and down into the mediastinum and, by rupture, into the pleural cavities.

4. Puncture of the jugular veins for diagnostic or therapeutic reasons should be done with caution to prevent tracheal injury.

2327 Grand Concourse (53).

Dr. Milton Helpern, Deputy Chief Medical Examiner, Office of the Chief Medical Examiner of the City of New York, performed both these autopsies.

Case Reports

INTRACRANIAL HEMORRHAGE AND ASEPTIC PURULENT MENINGITIS IN NEWBORN INFANTS

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AND
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WITHIN the last twenty years, two types of meningitis in infancy have been described. One is benign lymphocytic meningitis and the other is aseptic purulent meningitis.

As regards their causation, two schools of thought exist. Several authors [1] favor a unitary conception, while others [2] believe there are a plurality of causes. From our own experience in the past fifteen years, we are inclined toward accepting the latter point of view, at least as far as this region is concerned, because the second type of meningitis has been seen here rarely, while the former has been observed not infrequently. Fifty-six patients with benign lymphocytic meningitis have been treated by us.

Conditions here obviously are entirely different from those prevailing in Europe.

The case reported in this paper is that of a baby with aseptic purulent meningitis, and it was remarkable in these respects: First, the condition occurred immediately subsequent to an intracranial hemorrhage; second, no increase in temperature above normal was observed in its entire course; third, the cerebrospinal fluid obtained by puncture of the fontanel was hemorrhagic (simultaneous lumbar puncture gave evidence of a suppurative process), and, fourth, an autopsy was performed.

REPORT OF CASE

The patient, T. K., was 1 month of age, having been born Dec. 19, 1943. The weight at birth was 3,560 Gm. On the fourth day of life, a slight convulsion of the facial muscles on the left side occurred. On the seventh day, when she was brought to our hospital by her mother for consultation, she was in a good state of nutrition. The fontanel was large, measuring 2 by 2 cm. Nothing abnormal was observed at that time.

On Jan. 29, 1944, the mother brought her again to the hospital, with the complaint of frequent vomiting, which was noticed on the previous day. Because of the possibility of hydrocephalus, she was admitted to our hospital. Lumbar puncture, which was done on the next day, to our surprise showed a highly

1. Schiff, E.: Monatsschr. f. Kinderh. **48**:434, 1930. Akasawa, T.: J. Orient. Med. **20**:31, 1934. Glanzmann, E., and Heller, D.: Schweiz. med. Wchnschr. **66**:541, 1936.

2. (*a*) Hassler: Med. Welt. **5**:1658, 1930. (*b*) Fanconi: Ergebn. d. inn. Med. u. Kinderh. **57**:1939. (*c*) Pelle and Massot: Ztschr. f. Kinderh. **34**:1938.

turbid cerebrospinal fluid that on the following day exhibited apparent xanthochromia with a heavy sedimentation of pus at the bottom of the test tube. No bacteria were seen on staining. Fresh specimens were taken on two subsequent occasions and referred to Prof. Hiroki, of the Bacteriological Institute of the Manchuria Medical College, for bacteriologic examination. Results of cultures and inoculation into mice were negative for pathogenic organisms.

On the following days the general condition of patient was much improved. Owing to the remarkable difference in the liquid obtained by fontanel and lumbar puncture, a passage test (*Übergangversuch*) was made with "akzisol" at the beginning of the fourth week. The results were as follows: Five-tenths cubic centimeter of "akzisol" was injected by puncture of the fontanel (ventricular puncture was unsuccessful). A stain of the spinal fluid prepared fifteen minutes later was negative for pathogenic organisms, but after twenty-one minutes it had become positive. This seemed to show that communication was not inhibited. The spinal fluid at that time was no longer suppurative, but slightly opalescent. The albumin content was increased from 16 to 40 mg. per hundred cubic centimeters. The body weight had increased to 4,990 Gm. On March 5, the baby left the hospital.

In the seventh week she began to vomit again and bulging of the fontanel was noticed. Liquid obtained by both fontanel and lumbar puncture was macroscopically much improved, but microscopically the following differences were seen:

Type of Puncture	Xantho-chromia	Number of Polymorpho-nuclear Cells	Number of Lymphocytes	Number of Red Blood Corpuscles	Albumin, Mg./100 Cc.
Fontanel.....	+	16	64	192	60
Lumbar.....	+	352	75	1,472	33

At the end of April, when she was 4 months old, the patient had smallpox; from that time her head became larger, measuring 47.8 cm. in circumference, while the circumference of the chest was 38.8 cm. The large fontanel was 5 by 5 cm. Repeated ventricular puncture yielded a total of 540 cc. The nature of the cerebrospinal fluid was much improved, showing 2 polymorphonuclear cells, 7 lymphocytes, 70 red blood corpuscles, a 3 plus reaction to the Pandy test and an albumin content of 0.27 Gm. per hundred cubic centimeters. A diagnosis of hydrocephalus seemed justified. Pneumoencephalography showed enormously enlarged ventricles. Subsequently the patient lost appetite, became comatose and breathed irregularly. She died on June 25.

Autopsy was performed twenty-four hours post mortem. A precise examination of the brain and spinal cord was therefore impossible. There was no adhesion, scar formation or suppurative lesion, except severe internal hydrocephalus.

COMMENT

From the aforementioned clinical findings and summarized anatomic observations, we draw attention to the following facts: The convulsions of the facial muscles, which were observed on the fourth day, and the characteristic changes of the cerebrospinal fluid demonstrate the existence of intracranial hemorrhage.

Whether such pathologic changes bear a causal relation to each other or are coincidental is a problem which would be worth solving. We are inclined to believe in a causal connection between them, because in reviewing the literature we find case reports resembling the present one.

In 1936, Pelle and Massot [2c] described in their nomenclature of *"méningites aiguës curables"* a benign form involving bleeding of the brain. In 1938, Lombard [3] reported 2 cases of aseptic purulent meningitis which occurred after a basilar skull fracture. In 1939, Frontali [4] published an account of the same type of meningitis after trauma to the skull and embolus of the cerebral sinus.

In view of the literature cited, the case reported in this paper seems to contribute a casuistic supplement to a theory favoring a causal connection between these two conditions, especially since no fever was exhibited throughout the entire course of illness, and the condition continued more or less favorable in its further development, notwithstanding the extremely turbid fluid. A new problem seems to pose itself: whether formation of pus inevitably indicates the simultaneous existence of an inflammatory process, at least when it occurs in the cerebrospinal cavity after intracranial hemorrhage.

Care of Prof. Hattori, Children's Clinic, Medical Faculty, Kyoto Imperial University, Kyoto, Japan.

3. Lombard: Ztschr. f. Kinderh. **34**:1938.
4. Frontali: Ztschr. f. Kinderh. **37**:1940.

STERILE ABSCESS IN BOTH BUTTOCKS

Secondary to Injection of Penicillin in Sesame Oil

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REPORTS of abscess formation due to intramuscular injection of penicillin in sesame oil are uncommon enough to warrant the report of a single case.

REPORT OF A CASE

J. C., the 12 year old son of a physician, received 200,000 units of penicillin in an emulsifying vehicle of sesame oil; 1 cc. (100,000 units) was injected intramuscularly into each buttock for streptococcic pharyngitis six weeks prior to his admission to the hospital. For ten days following administration there was bilateral tenderness and swelling. The temperature at that time was 104 F. (orally); the white blood cell count was 16,400, with 71 per cent polymorphonuclear leukocytes and 21 per cent lymphocytes. The patient remained at home in bed with an elevation in temperature for two weeks. Treatment at home consisted of hot sitz baths two times daily. There was slow improvement until four days prior to his admission to the hospital, when the temperature again became elevated.

The past history and the family history revealed routine immunizations and childhood exanthems without sequelae. A strong incidence of allergy was present in the family, but no such manifestations had been noted previously in this patient.

Physical examination on his admission showed a well developed, well nourished, white boy, not acutely ill but in moderate discomfort when walking. Results of the entire examination were normal except for prominently swollen, tender, indurated, reddened areas over both buttocks. Each measured approximately 8 cm. in diameter, and the border was easily outlined by palpation.

Laboratory studies on his admission showed a white blood cell count of 28,000, with 78 per cent polymorphonuclear leukocytes. The erythrocyte sedimentation rate at 15 minutes was 13 mm., at 30 minutes, 25 mm. and at 1 hour, 39 mm.

Course in the Hospital.—Conservative treatment with continuous application of warm, moist compresses was carried out. On the eighth day in the hospital (seven weeks after the injection) the abscess of the left buttock ruptured spontaneously and drained approximately 4 ounces (120 cc.) of bloody material mixed with droplets of oil. Nine days later, the abscess on the right was opened and approximately 3 ounces (90 cc.) of thick, cloudy, serosanguineous fluid mixed with oil droplets was obtained. The culture of the material from the left buttock was sterile. The culture of material from the right was sterile after twenty-four hours, and in forty-eight hours showed nonhemolytic streptococci (contamination?).

The patient's course was one of rapid improvement following drainage, and he was discharged thirteen days after rupture of the abscess on the left (five days after incision and drainage of that on the right) or on his twenty-first day in the

From the Milwaukee Children's Hospital.

hospital. His loss of weight during illness was 30 pounds (13.6 Kg.). He became ambulatory. Slight drainage continued for about a month, when the wound healed. The patient is again a robust, active boy.

SUMMARY

A report on a patient with a sterile abscess in each buttock, following intramuscular administration of penicillin in sesame oil, is presented. The clinical manifestations were fever, tenderness and induration. Treatment consisted of continuous application of moist, warm compresses. One abscess ruptured spontaneously and one was incised and drained; both contained droplets of oil in the drainage fluid.

The boy made an uneventful recovery after being confined to bed for eleven and one-half weeks because of pain in the areas of injection.

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NEPHROLITHIASIS WITH RENAL TUBULAR FAILURE

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FAILURE of a single function of the renal tubules has been a well recognized entity. Thus, Thorn and his associates [1] reported a case of "salt-losing nephritis" which so closely simulated adrenocortical hypofunction (Addison's disease) that it went unrecognized for some time. Albright and his co-workers [2] gathered together and reported 9 cases of nephrolithiasis and nephrocalcinosis in which they showed that the primary defect lay in the inability of the renal tubules to form ammonia. This resulted in the loss of fixed base, with precipitation of calcium salts in the tubules and renal pelves. Loss of fixed base other than calcium may occur; potassium deficiency with resulting paralysis has been reported by Brown, Currens and Marchand [3] in a case of chronic nephritis in which tubular formation of ammonia had failed.

The case presented herein shows many of the features of those described by Albright and his associates.

REPORT OF A CASE

J. A., a North American Indian boy 14 months of age, entered the Children's Hospital, Winnipeg, Manitoba, Canada, on Oct. 28, 1947 because he had passed several stones by the urethra for the past eight months. Little other history was available as he had been brought in by plane with an escort from northern Manitoba, and the party had no additional information on him. It was learned, however, that his diet consisted of the "standard fare" of the Indians in this region, with no supplements of vitamins C or D.

He weighed 23.5 pounds (10,659 Gm.) and was 30.5 inches (77.5 cm.) in height. Results of his examination were essentially normal. There was no clinical evidence of rickets.

From the Children's Hospital and the Department of Pediatrics, University of Manitoba Faculty of Medicine.

1. Thorn, G.; Koepf, G. F., and Clinton, M., Jr.: Renal Failure Simulating Adrenocortical Insufficiency, New England J. Med. **34**:76, 1944.

2. Albright, F.; Burnett, C. H.; Parsons, W.; Riefenstein, E. C., Jr., and Roos, A.: Osteomalacia and Late Rickets, Medicine **25**:399, 1946.

3. Brown, M. R.; Currens, J. H., and Marchand, J.: Muscular Paralysis and Electrocardiographic Abnormalities Resulting from Potassium Loss in Chronic Nephritis, J. A. M. A. **124**:545 (Feb. 26) 1944.

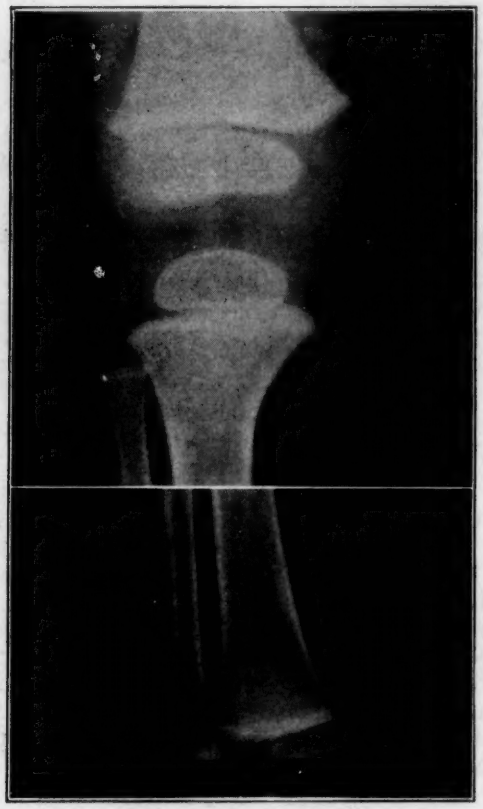

Fig. 1.—Roentgenograms of the knee (upper part) and of the lower end of the fibula and tibia (lower part), showing no evidence of rickets.

Fig. 2.—Roentgenogram of renal area showing stones in both renal pelves.

Roentgenograms of his long bones (fig. 1) showed evidence of arrest of growth but no sign of rickets. Flat films of the abdomen showed calculi in both renal areas (fig. 2) but no evidence of nephrocalcinosis and no calculi in the bladder.

A calculus he passed was examined. It contained calcium, urates, phosphates and oxalates.

The urine had a specific gravity of 1.018 on the casual specimen and contained neither albumin nor cells. The Sulkowitch test gave a milky precipitate. There were no cystine crystals. Culture of the urine yielded no organisms.

The carbon dioxide content of venous blood was 19.5 milliequivalents per liter; chlorides measured 106.2 milliequivalents per liter, with 10 mg. of calcium, 4 mg. of phosphorus and 7.9 Gm. of serum protein, per hundred cubic centimeters. Serum alkaline phosphatase was 13.8 King units. The nonprotein nitrogen level was 43.5 mg. per hundred cubic centimeters. Phenolsulfonphthalein excretion (by the intramuscular method) was 0.9 per cent in one hour and 49.2 per cent in two hours.

The low carbon dioxide content and relatively high chloride level led us to suspect that the child had renal acidosis, possibly due to the inability of the renal

Metabolic Study on a Child with Renal Tubular Failure: Effect of Acid, Alkaline and Neutral Ash Diets

	Period 1 (Neutral Ash Diet), mEq.	Period 2 (Acid Ash Diet), mEq.	Period 3 (Alkaline Ash Diet), mEq.
Blood carbon dioxide	19.4	16.9	22.0
Blood chlorides	105.8	113.6	95.2
Urinary calcium output per 24 hr.	1.8	3.5	0.6
Urinary ammonia output per 24 hr.	23.8	12.8	15.8

tubules to form ammonia. With this in mind, we undertook to study his urinary ammonia and calcium output and the blood carbon dioxide and chloride content over three metabolic periods.

Period 1 was a neutral ash regimen of three days. The calcium intake in this period was 0.8 Gm. per twenty-four hours. Period 2 was an acid ash regimen plus 1 Gm. of ammonium chloride in twenty-four hours. After ten days on this regimen, studies were made (table). This regimen provided 1.0 Gm. of calcium per twenty-four hours. Period 3 was an alkaline ash regimen providing 0.9 Gm. of calcium in twenty-four hours. In addition, during period 3, 3,000 units of vitamin D_2 was given each day and 75 cc. of a mixture of 140 Gm. of citric acid and 98 Gm. of sodium citrate made up to 1,000 cc. with water. Studies were made after five days on this regimen. The results of the study are recorded in the table.

COMMENT

It is seen from the table that the renal tubules failed to increase the ammonia output in response to an acid ash diet. The calcium output on this regimen is high, as is the output on the neutral regimen. The alkaline ash (period 3) reduces calcium output considerably, and on this routine the patient passed the stones present in the renal pelves and had formed no new ones after four months.

It is difficult to understand why the child failed to show rickets. This is attributed by Dr. Fuller Albright [4] to the fact that the serum phosphorus failed to fall to a low level. This, in turn, in his opinion, was due to the fact that the loss of calcium in the urine was being taken care of by an adequate calcium intake and absorption. Hence, lowered serum calcium levels failed to occur and parathyroid activity was not stimulated to lower the phosphorus level.

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Dr. Fuller Albright advised in this case. Dr. Bruce Chown, Dr. Paul Green and Miss Beth Gourlay of the Children's Hospital assisted in this study.

4. Albright, F.: Personal communication to the authors.

MULTIPLE CALCAREOUS DEPOSITS IN THE INTESTINAL TRACT OF THE NEWBORN

Report of a Case Associated with Stenosis of the Ileum

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CALCIUM deposits occurring in the meconium of the newborn, under certain pathologic conditions, have been frequently reported. Such observations have usually been made on infants with meconium ileus and peritonitis, the calcified material existing as yellowish flakes in the peritoneal cavity or being plastered to the intestine and various viscera. Rarely has there been any mention of the occurrence of calcification within the intestinal tract, and even in these cases there has always been an accompanying perforation of the intestine with local or general peritonitis.

The case which we wish to present we believe is unique in that the infant exhibited extensive calcification of the intestinal contents at birth without any evidence of perforation or concomitant peritonitis.

Abt,[1] in 1931, summarized the literature on fetal peritonitis and included in his manuscript a case reported by Dubler[2] in 1888, the lesion in which was described as a curious cyst in the abdomen of a newborn infant, which, in his opinion, was due to the intrauterine perforation of the descending colon. The cyst contained meconium which was calcified and walled off, so that relative healing of the rupture had taken place.

Neuhauser,[3] in 1944, drew attention to the calcified plaques in the peritoneal cavity of newborn infants with meconium ileus and peritonitis as demonstrated on roentgenograms. He included reports on 3 infants, 1 of whom exhibited calcium deposits within the lumen of the bowel. This infant had atresia of the duodenum and accompanying omphalocele. At operation the omphalocele was observed to contain portions of jejunum and ileum which were excised because of strangulation. Examination revealed calcium deposits within the lumen and in the wall of

1. Abt., I. A.: Fetal peritonitis, M. Clin. North America **15**:611-622 (Nov.) 1931.

2. Dubler, A.: Eine eigenthümliche Cyste in der Bauchhöhle eines Neugebornen, Arch. f. path. Anat. **111**:567-574, 1888.

3. Neuhauser, E. B. D.: The Roentgen Diagnosis of Fetal Meconium Peritonitis, Am. J. Roentgenol. **51**:421-425 (April) 1944.

the bowel and a small deposit on the peritoneal surface, with extensive fetal peritonitis.

Kraatz [4] reported a perforation of the small intestine with fecal concretions as an unusual cause of death in a newborn infant, but he probably referred to a child with meconium ileus with perforation.

Enteroliths containing calcium are occasionally seen, such as that reported by Miller and Neff [5] in a breast-fed infant 8 months of age, but such depositions of calcium are in no way comparable with those seen in the following case.

REPORT OF CASE

R. M. W., a Negro woman, sextigravida and quartipara, was admitted to the obstetric service of Grady Memorial Hospital, Atlanta, Ga., on April 14, 1947, at term, in early labor. Her reaction to the Kahn test was negative. Her last menstrual period was Aug. 14, 1946. There had been no toxic symptoms, and pregnancy was uncomplicated, except for polyhydramnios. This was first noticed in December 1946. She was delivered of a 3,360 Gm. male infant by spontaneous, controlled right occipitoanterior mechanism, six hours after her admission. There was some dystocia due to the enlarged abdomen of the infant. The infant breathed and cried immediately, but respirations were weak and irregular after they were established, and his general condition seemed poor. He was placed in an incubator and given oxygen. Examination showed a sluggish infant with slight cyanosis and a tremendously enlarged abdomen. The heart rate was 160 per minute; no murmurs were heard. The breath sounds were fairly good throughout the pulmonary fields. The abdominal enlargement appeared to be caused by fluid. Sounds on percussion were dull throughout, except in the left upper quadrant. No masses were felt. Rectal examination revealed no abnormality, and apparently normal meconium was recovered on the examining finger. Farber's test on this failed to show any cornified epithelial cells.

A roentgenogram taken one hour after birth (fig. 1) showed innumerable calcium deposits, measuring 1 to 4 mm. in diameter, scattered throughout the greatly distended abdomen. These deposits were interpreted at the time as probably due to a massive meconium peritonitis. Abdominal paracentesis yielded 5 cc. of straw-colored fluid, which proved to be sterile on culture. Roentgenograms showed no evidence of pathologic changes in bone.

At 6 hours of age, the infant began to vomit bile-stained fluid containing a moderate amount of mucus. A roentgenogram of the abdomen at 8 hours of age showed the same calcareous deposits and moderate distention of the small intestine (fig. 2).

Because of the unusual findings and signs of an intestinal obstruction, an exploratory laparotomy seemed indicated. This was done approximately eighteen hours after birth. The operative note in part follows.

The peritoneum was opened through a right paramedian incision and appeared normal. The small intestine was observed to be greatly dilated with fluid and gas. Examination of the ileum revealed a stenosis of the terminal 8 to 10 cm. The ileum was opened proximal to the stenosis and a suction tip inserted through a purse string suture. The small intestine was emptied of a large amount of

4. Kraatz, H.: Dünndarmperforation über einem Kotstein mit Peritonitis als seltene Todesursache beim Neugeborenen, Zentralbl. f. Gynäk. **61**:1648-1650 (July 10) 1937.

5. Miller, E. L., and Neff, F. C.: Enterolith as Cause of Chronic Obstipation in a Breast-Fed Infant, Am. J. Dis. Child. **27**:105-109 (Feb.) 1924.

greenish gray material that contained numerous small, jelly-bean-like masses, each with a small hard center. After emptying the intestine, this opening was closed and an ileotransverse colostomy opening in continuity was made.

Roentgenologic examination of the abdomen after operation showed a notable decrease in the number of calcium deposits (fig. 3). A sample of the fluid withdrawn from the intestine was placed in test tubes and, along with tap water, was examined roentgenographically (fig. 4). This showed the fluid to contain the calcium deposits seen on previous films made of the abdomen. The department of pathology reported that the material contained calcium, epithelial cells and debris.

Fig. 1.—Roentgenogram taken at 1 hour of age, showing innumerable calcium deposits scattered through greatly distended abdomen.

The infant was placed on supportive measures, including oxygen and penicillin and fluids subcutaneously, but he did poorly and died approximately thirty hours after operation, forty-eight hours after birth.

Autopsy Observations.—An autopsy was performed thirty-seven hours after death. The following excerpts from the protocol seem pertinent.

Gastrointestinal Tract: The esophagus was not remarkable. The cardia and pylorus of the stomach appeared normal. The gastric mucosa was smooth and the rugae were not remarkable except for several dark hemorrhagic areas, measuring 3 to 8 mm. across. Similar areas were also noted in the serosa of the stomach. The duodenum did not appear remarkable; however, its distal end was distended to a diameter of 3 cm., and the jejunum and ileum were similarly

distended to a diameter of 5 or 6 cm. up to a point 5 cm. proximal to the ileocecal valve. At this point, the terminal part of the ileum became extremely stenotic. As previously noted, there was an ileotransverse colostomy opening located 11.5 cm. above the ileocecal valve. Surrounding this anastomosis were profuse hemorrhagic fibrinous exudate and adhesions. The anastomosis measured 3 cm. in length. The tissues and sutures appeared intact.

In order to evaluate the patency of the colostomy opening and stenosis, water was forced into the lumen of the ileum above the colostomy opening; the lumen of the intestine was occluded in such a manner as to route the water through the colostomy opening and then through the stenosis. This procedure demonstrated patency of the colostomy opening but complete obstruction in the area of the stenosis of the terminal portion of the ileum. The mucosa of the small intestine was generally hyperemic and edematous; however, the wall of the

Fig. 2.—Roentgenograms taken at 8 hours of age: *A*, anteroposterior view, showing extensive calcium deposits in small and large bowel; *B*, lateral view, showing extensive calcium deposits throughout abdomen.

area of stenosis was thin but strong and the diameter was uniform, being 0.5 mm. The contents of stomach, duodenum and small intestine were yellowish brown and, at times, reddish, gelatinous and mucoid. Also seen in the duodenum and small intestine were numerous firm, round concretions, varying from 1 to 3 mm. in diameter. The outer surfaces of these concretions were clear and whitish and appeared to contain a black or brown opaque core. The concretions cut with considerable difficulty. All the concretions were lying free in the mucoid contents of the intestine. None was attached in any way to the mucosa.

Pancreas: The pancreas weighed 1.5 Gm. It was of the usual size, shape and consistency. On cut surface the lobulations were prominent and the ducts were patent.

Liver: The liver weighed 85 Gm. Its surface was smooth, glistening and reddish brown. The cut sections were dark reddish brown. The lobular architecture was made out with difficulty. The liver was firm. The gallbladder contained 5 to 7 cc. of greenish mucoid substance. The ducts appeared patent, though small. The mucosal wall was thin and smooth. The extrahepatic ducts were patent.

Adrenal Glands: The left adrenal gland weighed 7 Gm. and the right, 5 Gm. No abnormalities were noted on gross examination.

Kidneys: The left kidney weighed 7.2 Gm. and the right, 6.4 Gm. The capsules separated easily and revealed a smooth, yellowish brown cortical surface. The thickness of the cortex was 2 to 3 mm. The striations of the pyramids

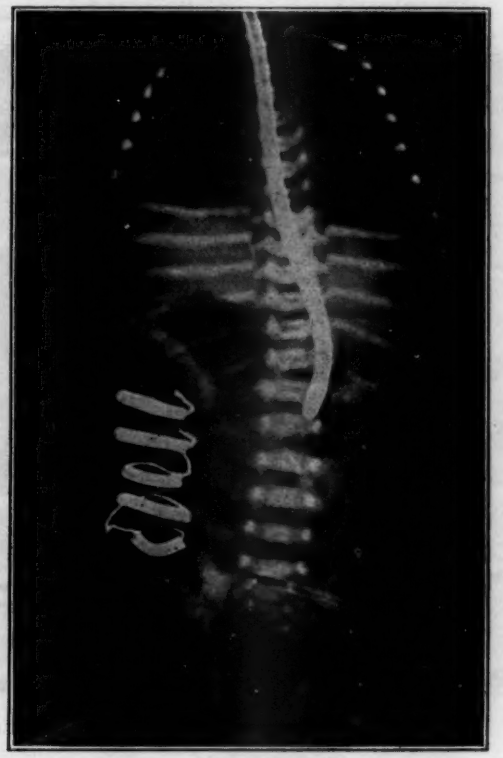

Fig. 3.—Roentgenogram of abdomen taken after operation and removal of much of calcium deposits in small intestine.

were prominent and the glomeruli were discernible as tiny red dots. The pelves and ureters were not remarkable.

Pelvic Organs: The bladder contained approximately 10 cc. of clear yellow urine. The mucosa appeared slightly hyperemic in the area of the trigone but was otherwise not remarkable. The ureteral orifices were small but patent. The prostate, seminal vesicles and testes were not remarkable.

Vascular System: The aorta was normal in elasticity. Its intima was not remarkable.

Lymphatic System: The lymphatic system revealed no abnormalities.

Thyroid: The thyroid gland weighed 0.9 Gm.

Thymus: The thymus gland weighed 4.1 Gm. and was pale brown.

Bone Marrow: The bone marrow was dark red and appeared cellular.

Brain: The brain weighed 300 Gm. No abnormalities were noted in the scalp, cranium, dura or dural sinuses. The brain was symmetric. Its convolutions and sulci were not remarkable. The meningeal vessels appeared normal.

Pituitary: The pituitary measured approximately 3 mm. in diameter. It was soft. The sella turcica appeared to be within normal limits.

Microscopic Examination.—The microscopic observations were as follows:

Heart: The myocardium was moderately congested. The muscles did not appear remarkable. There was extensive subepicardial hemorrhage.

Lungs: The lungs showed pronounced atelectasis which appeared to be primary in type. Many of the alveoli contained desquamated squamous epithelial

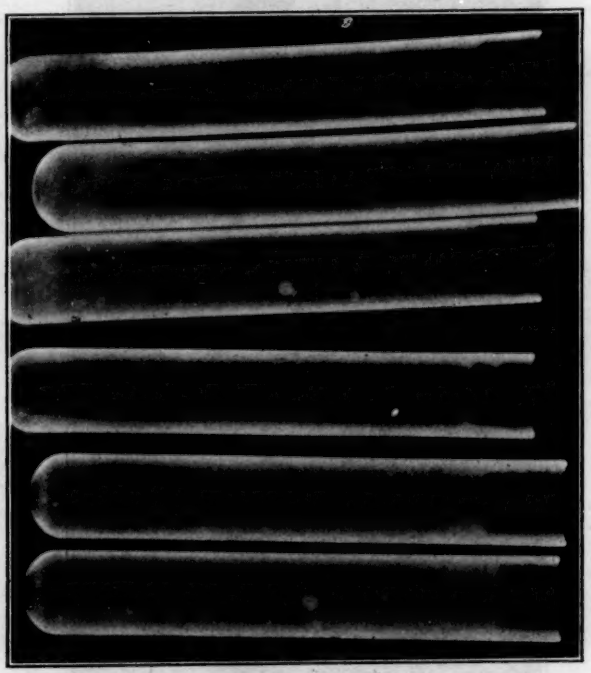

Fig. 4.—Roentgenogram of material removed from small intestine as compared with tap water.

cells suggestive of the contents of the amniotic sac. A few of the alveoli contained mononuclear cells which appeared to be alveolar lining cells, and occasional polymorphonuclear leukocytes were noted. There was also severe congestion near the pleural surfaces but no hemorrhages were noted.

Spleen: The red pulp was extremely congested. The trabeculae were not unduly prominent. The malpighian corpuscles appeared somewhat smaller than normal. Numerous areas of erythropoiesis were noted within the red pulp.

Gastrointestinal Tract: One section represented the ileum above the area of stenosis. The submucosa was congested and edematous. The muscle layers appeared entirely normal. Covering the serosal surface was a small amount of acute fibrinous exudate containing polymorphonuclear leukocytes. Two sections represented the ileum in the area of stenosis. Here, the principal finding was

decided atrophy of the muscle layers; however, both transverse and longitudinal musculature could be clearly made out. The submucosa was greatly compressed but was not otherwise remarkable. There were occasional mononuclear cells in this area but no true connective tissue proliferation was present. One section showed several of the concretions which were described in the intestinal contents. These appeared to consist of a central mass of necrotic cellular elements, surrounded by layers of mucus. The degree of necrosis of the central cellular mass made identification difficult; however, some stratified squamous epithelial cells could be identified. In other structures, the central cells suggested degenerated gastrointestinal columnar epithelial cells. Several areas of calcification were noted in the central areas, and some calcification was also observed beneath the mucosa covering the concretions.

Pancreas: The only significant observation was congestion. The pancreatic ducts appeared to be normal.

Liver: The liver was moderately congested, both in the portal and in the central areas. Aside from numerous areas of focal erythropoiesis, there were no other observations.

Adrenal Glands: The adrenal glands showed only congestion and moderate autolysis.

Kidneys: Except for pronounced congestion and occasional extravasation of red blood cells, the only observation was postmortem autolysis.

Thymus: The thymus gland appeared normal for an infant this age.

Bone Marrow: The bone marrow section was taken from a lumbar vertebra and was not remarkable.

Brain: The sections of brain showed only congestion of the small blood vessels and poor fixation.

Pathologist's Summary.—The principal observation at autopsy was a severe stenosis of the distal 5 cm. of the ileum. Microscopic examination of the stenotic portion of the ileum showed pronounced atrophy of the muscular coats and compression of the submucosa. An ileotransverse colostomy opening was seen 11.5 cm. above the ileocecal valve. The anastomosis appeared to be in good condition, but there was an acute fibrinous peritonitis in the surrounding tissues. Numerous small concretions were noted in the intestinal and gastric contents. These appeared to consist of a central necrotic mass of cells, some of which were suggestive of squamous epithelium, others of degenerative gastrointestinal columnar epithelium. The central mass of cells was surrounded by extensive mucus. Calcification of the concretions was prominent.

COMMENT

The histologic studies of the gastrointestinal tract indicated that although the obstruction in the terminal part of the ileum at the time of autopsy appeared mechanically complete, it was actually a stenosis and not a true atresia. This observation seems strengthened by the roentgenogram shown in figure *2A,* in which calcium deposits are distinctly seen in the pelvis and must be in the large bowel beyond the stenotic area.

The cause for the deposition of calcium in the intestinal tract is obscure.

Unfortunately, calcium studies on the blood of mother and child were not carried out. However, the bony structure of the infant showed no evidence of decalcification, which one might expect to see in metabolic disturbances, such as hyperparathyroid disease.

It seems likely that the deposition of calcium in the intestinal tract of this infant was due to the local condition existing in the ileum and not to any systemic disease in either mother or child.

The meconium of the normal newborn infant is slightly acid in reaction. It contains dead epithelial cells from the intestinal tract and skin of the fetus, secretions from the stomach, intestine, liver and pancreas, calcium soaps and cholesterol crystals and amniotic fluid, in which is found fatty material from the sebaceous glands of the infant, squamous epithelial cells and lanugo.

Amniotic fluid between the seventh and the ninth months of fetal life is said to contain the following constituents per hundred cubic centimeters:[6] calcium, 5.46 mg.; sugar, 19 mg.; phosphorus, 3.1 mg.; protein, 0.53 Gm.; nonprotein nitrogen, 24.25 mg., and uric acid, 4.54 mg.

There appear, then, to be two sources of calcium: that swallowed in the amniotic fluid and that excreted into the small intestine directly from the blood of the fetus. In man, on an ordinary mixed diet, the calcium of the feces amounts to 0.4 to 0.8 Gm. daily. This, though partly endogenous, is mainly the unabsorbable calcium of the food.

Boikan,[7] in a discussion of meconium peritonitis, stated that

> . . . calcification of the meconium is, no doubt, due to the precipitation of the calcium of the tissue fluids and the blood by the broken down fatty constituents.

Under certain pathologic conditions calcium is known to be deposited in soft tissue.

> Dystrophic calcification is the term applied to the deposition of calcium salts in dead, dying or chronically inflamed tissues and in areas of fatty or hyaline degeneration. Thus areas of necrosis, infarcts, scar tissue, caseous tuberculous areas and degenerative nerve cells, tend to undergo calcification. . . . The factors determining the deposition of calcium salts in devitalized tissues are obscure. It has been suggested that since CO_2 production in such tissues is minimal or entirely absent, they will have a more alkaline reaction; this, of course, would tend to cause the deposition of calcium salts.[8]

Certain conditions conducive to the deposition of calcium were known to exist in this case, chief of which was the presence of calcium and fats in considerable amounts in the intestinal tract. Whether a change in the p_H of the intestinal contents toward alkalinity was the determining factor cannot be stated. Unfortunately, the reaction of the contents at the time of operation was not determined.

Since the occurrence of stenoses and atresias of the bowel is encountered fairly frequently in the newborn without the deposition of calcium, it seems that some rare and as yet unknown factor existed in this case to account for the unique observations.

33 Ponce de Leon Avenue, N. E. (3).

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6. Cantarow, A.; Stuckert, T. H., and Davis, R. C.: Chemical Composition of the Amniotic Fluid, Surg., Gynec. & Obst. **57**:63-70 (July) 1933.

7. Boikan, W. S.: Meconium Peritonitis from Spontaneous Perforation of the Ileum in Utero, Arch. Path. **9**:1164-1183 (June) 1930.

8. Best, C. H., and Taylor, N. B.: Physiological Basis of Medical Practice, ed. 4, Baltimore, Williams & Wilkins Company, 1945, p. 719.

Progress in Pediatrics

THROMBOPENIC PURPURA IN THE NEWBORN

Review of the Literature and Report of Six Cases

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DURING the past three years, 6 infants with generalized cutaneous purpura during the newborn period have come under observation. Four of the infants have shown early severe thrombopenia. This fact is of interest, since not more than 3 cases have been reported previously from any one institution. Reported cases of this clinical entity have long appeared in the literature. The recent increased frequency of these reports focuses added attention in their direction. The literature reveals considerable divergence of opinion regarding the number of cases reported, the terminology, the diagnostic criteria, etiology and classification. It is unfortunate that the clinical and laboratory data in many cases are incomplete.

This paper presents a detailed study of the cases previously reported, with the addition of 6 new cases. It is our hope to clarify somewhat the present status of this disease picture and to remove some of the existing confusion. Thus far, there has been no complete review of the 34 cases reported previously. Schefrin and Shechtman,[1] in 1945, referred to 19 cases, and Waters,[2] in 1946, mentioned 17. The cases summarized in this study have usually been entered in the literature under the general category of purpura in the newborn period.

CASES PREVIOUSLY REPORTED

De Lingen,[3] Dohrn,[4] Hanot and Luzet,[5] Glenn[6] and Zangemeister[7] reported cases of purpura in the newborn manifested by either cutaneous

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1. Schefrin, A. E., and Shechtman, A.: Congenital Thrombopenia, Am. J. Dis. Child. **70**:29 (July) 1945.

2. Waters, H. W.: Neonatal Thrombocytopenic Purpura, Am. J. Obst. & Gynec. **51**:708, 1946.

3. de Lingen, J. H.: De quinque neonatorum morbis notatu dignis, Berlin, typ. Bruschckianis, 1828.

4. Dohrn, E.: Ein Fall von Morbus maculosus Werlhofii übertragen von der Mutter auf die Frucht, Arch. f. Gynæk. **6**:486, 1873.

(Footnotes continued on next page)

or visceral hemorrhage. No laboratory work was done in these early cases. De Lingen's interesting dissertation, in 1828, recorded 5 cases. The case of Hanot and Luzet represented purpura associated with a streptococcic septicemia. The mother in Glenn's report had occasional attacks of epistaxis while pregnant. In Zangemeister's case the mother suffered from purpura and bleeding from the mucous membranes. Diehl,[8] in 1899, reported a case in which a dead fetus, about 5 months of age, was delivered following a brief febrile illness. The mother then had purpura and severe thrombopenia and died quietly four days later. At necropsy, both mother and infant showed cutaneous and visceral bleeding.

In Rushmore's[9] case, the fetus, spontaneously miscarried, showed no evidence of purpura and no autopsy was performed. Previous papers have credited this author with reporting 7 cases. His report included the cases of Hanot and Luzet,[5] Vignes and Stiassnie[10] and Wiener[11] in addition to his own, and these cannot properly be included as true cases. The case reports of Vignes and Stiassnie and Wiener mentioned no evidence of purpura in the infants. Rushmore's paper, therefore, actually includes 3 cases in which the infant had purpura.

The infant in Greenwald and Sherman's report[12] underwent circumcision uneventfully but on the tenth day showed purpura and hemorrhage. The child died, autopsy revealing visceral chronic passive congestion and bone marrow with scant megakaryocytes. In Conti's[13] case a mother with a history of thrombopenic purpura died of subarachnoid hemorrhage in the fifth month of pregnancy during an acute episode of hemorrhage. The fetus showed no cutaneous hemorrhage

5. Hanot, V., and Luzet, C.: Note sur le purpura à streptocoques au cours de la méningite cérébrospinale streptococciene, Arch. de méd. exper. et d'anat. path. **2**:772, 1890.

6. Glenn, J. H.: Notes on a Case of Purpura in the Newborn Period, Dublin J. M. Sc. **96**:68, 1893.

7. Zangemeister, E.: Eine Komplikation von Schwangerschaft und Geburt mit einer Form von hämorrhagischer Erkrankung, Ztschr. f. Geburtsh. u. Gynäk. **39**:593, 1898.

8. Diehl, J. C.: Ueber Purpura in Puerperio, Ztschr. f. Geburtsh. u. Gynäk. **41**:218, 1899.

9. Rushmore, S.: Purpura as a Complication of Pregnancy, Am. J. Obst. & Gynec. **10**:553, 1925.

10. Vignes and Stiassnie: Purpura récidivant au cours de trois gestations successives, Bull. Soc. d'obst. et de gynéc. **10**:8, 1921.

11. Wiener, M.: Ueber hämorrhagische Erkrankungen bei Schwangeren und Wöchnerinnen, Arch. f. Gynäk. **31**:281, 1887.

12. Greenwald, H. M., and Sherman, I.: Congenital Essential Thrombocytopenia, Am. J. Dis. Child. **38**:1245 (Dec.) 1929.

13. Conti, F.: Purpura in Pregnancy: Fatal Episode with Fetal Manifestations, Rassegna internaz. di clin. e terap. **14**:450, 1933.

but did have extensive meningeal hemorrhage. The femoral bone marrow showed normal megakaryocytes. It is impossible to say that the condition of this unborn fetus was a true case and, therefore, the report is omitted from the list of established cases. The infant in Siegler's [14] case had no external evidence of purpura, no laboratory work was done and no autopsy was performed. This case, previously included in some reports, cannot be considered a valid one. Schefrin and Shechtman reported the case of a child born with generalized cutaneous purpura who later had slight bleeding from the umbilical stump. Thrombopenia was the only abnormal laboratory finding. After six weeks, all findings were normal. The mother was normal, clinically and hematologically.

Davidson,[15] Urbanski and Hutner,[16] Whitney and Barritt,[17] Finn [18] and Talmadge and Berman [19] reported interesting cases of purpura in the newborn of mothers who previously had splenectomy performed. Thrombopenic purpura in twins was reported by Bayer [20] and Goldstein.[21] Bayer also reported a case wtih generalized petechiae and ecchymoses followed by moderate icterus, in which most of the laboratory data returned to normal within two months. Cases with a familial history of hemorrhagic diathesis have been discussed by Guttfreund,[22] Waters,[2] Sanford and his associates [23] and Patterson.[24]

14. Siegler, S. L.: Purpura Hemorrhagica Complicating Pregnancy, M. Rec. **139**:189, 1934.

15. Davidson, L. T.: Congenital Thrombopenia, Am. J. Dis. Child. **54**:1324 (Dec.) 1937. Polowe, D.: Splenectomy in Pregnancy Complicated by Thrombocytopenic Purpura Hemorrhagica: Report of a Successful Case, with a Review of the Literature, J. A. M. A. **124**:771 (March 18) 1944.

16. Urbanski, A. X., and Hutner, C. I.: Thrombopenic Purpura Complicating Pregnancy: Treatment by Splenectomy Resulting in Clinical Cure and Followed by Three Full Term Pregnancies, J. A. M. A. **120**:754 (Nov. 7) 1942.

17. Whitney, L. H., and Barritt, A. S., Jr.: Spontaneous and Hereditary Thrombopenic Purpura in a Mother and Two Sons, Am. J. Dis. Child. **64**:705 (Oct.) 1942.

18. Finn, W. F.: Thrombocytopenic Purpura in Pregnancy: Review of the Literature with a Report of Three Cases, Am. J. Obst. & Gynec. **48**:497, 1944.

19. Talmadge, J., and Berman, B.: Congenital Thrombocytopenic Purpura, J. Pediat. **30**:691, 1947.

20. Bayer, W.: Beitrag zu den hämorrhagischen Erkrankungen des Neugeborenen, Jahrb. f. Kinderh. **133**:222, 1931.

21. Goldstein, L. S.: Congenital Essential Thrombopenic Purpura: Report of Condition in Fraternal Twins, Am. J. Dis. Child. **73**:575 (May) 1947.

22. Guttfreund, A.: Zwei Fälle von Morbus Werlhof im Säuglingsalter, Monatsschr. f. Kinderh. **55**:436, 1933.

23. Sanford, H. N.; Leslie, E. I., and Crane, M. M.: Congenital Thrombocytopenia, Am. J. Dis. Child. **51**:1114 (May) 1936.

24. Patterson, W. B.: Thrombocytopenic Purpura in Pregnancy and in the Newborn, J. A. M. A. **130**:700 (March 16) 1946.

The paternal branch was involved in the first 2 case reports and the maternal in the latter. Other cases in which the mother had purpura in the past or during pregnancy were noted by Mosher,[25] Liebling,[26] Waltner,[27] Leschke and Wittkower [28] and Posner.[29] In Rodecurt's [30] case the mother gave only a history of excessive postpartum bleeding, and in Morrison and Samwick's [31] case of easy bruising.

REPORT OF CASES

CASES 1 AND 2.[32]—D. L., a 24 year old Polish-American woman, was admitted to the hospital in active labor, at term, on Nov. 25, 1945.

There had been four previous pregnancies in 1939, 1942, 1943 and 1944. All were terminated in normal fashion except the pregnancy of 1943. At that time first degree vaginal and third degree perineal lacerations occurred. Hemorrhage was profuse, and complete cessation of bleeding did not take place until the sixth day post partum. The female infant appeared normal at birth and progressed satisfactorily. On the ninth day both mother and infant were discharged from the hospital. Her past history was noncontributory, and the family history was negative for purpura or bleeding tendencies.

During the first trimester, the present pregnancy had been complicated by hypertension (blood pressure was 150 systolic and 90 diastolic), puffiness of the eyelids and face, edema of the ankles, feet and lower legs and albuminuria (3 plus). This subsided during the fourth month and did not reappear. During the sixth month she had a stubborn stomatitis for which sulfonamide therapy (18 tablets, a total of 6 Gm.) was used. The subsequent course through the last three months was uneventful, the blood pressure and urine remaining normal and the edema not recurring.

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25. Mosher, G. C.: The Complication of Purpura with Gestation, Surg., Gynec. & Obst. **36**:502, 1923.

26. Liebling, P.: Purpura Hemorrhagica Complicating Pregnancy, Am. J. Obst. & Gynec. **11**:847, 1926.

27. Waltner, K.: Ein Fall mit angeborenen manifesten Symptomen des Morbus Werlhofii, Jahrb. f. Kinderh. **56**:307, 1924.

28. Leschke, E., and Wittkower, E.: Die Werlhofsche Blutfleckenkrankheit (thrombopenische Purpura): Ein Beitrag zur Pathologie der Blutplättchen und Capillaren und zur Pathogenese der hämorrhagischen Diathese, Ztschr. f. klin. Med. **102**:649, 1925.

29. Posner, C. A.: Purpura Hemorrhagica Complicating the Puerperium, Am. J. Obst. & Gynec. **34**:155, 1937.

30. Rodecurt, M.: Ein besonderer Fall von universeller Purpura beim Neugeborenen, Zentralbl. f. Gynäk. **52**:241, 1928.

31. Morrison, M., and Samwick, A. A.: Congenital Essential Thrombocytopenic Purpura: Report of a Case and a Review of the Literature, Am. J. Dis. Child. **70**:115 (Aug.) 1945.

32. In all cases the following laboratory methods were used: the modified Dameshek method of counting thrombocytes (normal value, 400,000 to 900,000 cells); blood smears to corroborate the counts roughly; the Duke method for estimating bleeding time (normal value, 1 to 3 minutes); the Lee and White method for measuring clotting time (normal value, 2 to 5 minutes; the test tube method for determining clot retraction time, and the benzidine test for detecting occult blood.

At the time of this admission to the hospital no prelabor medication had been given. During the labor, vitamin K (4.8 mg.) was given, and a mixture of nitrous oxide and oxygen was administered during the second stage. After a labor of five and three-quarter hours, a male infant, weighing 4,580 Gm., was spontaneously delivered without difficulty.

The infant breathed immediately, was active and had a strong cry. At birth innumerable purpuric lesions, varying from a pinpoint to 0.5 cm. in diameter, were scattered over the surfaces of the skin. The lesions were most numerous on the face, neck, anterior part of the chest, groins, buttocks, popliteal regions, ankles, palms and forearms. Ecchymotic areas were present on the cheeks and around both ankles. The anterior fontanel was soft; the scleras were clear, and the nose, ears and lips were normal. Several petechial areas were present on the buccal surfaces and hard palate. The lungs were clear, the heart sounds distinct and no murmurs were heard. The spleen was not palpable and the edge of the liver was at the costal margin. There were two purpuric spots at the base of the umbilical cord. The baby appeared exceedingly vigorous and the color was excellent. The tourniquet test gave a strongly positive reaction.

Within six hours after birth, the following laboratory data were obtained on the child: Red blood cells numbered 4,360,000; the hemoglobin concentration was 14 Gm., the bleeding time, 5 minutes, the clotting time, 5 minutes and the clot retraction time, 8 hours. There were 65,700 thrombocytes. The Mazzini test gave a negative reaction. The blood was Rh positive and of type A, and culture was sterile.

A total of 9.6 mg. of vitamin K was given during the first twenty-four hours. At the end of that time laboratory reports showed 4,110,000 red blood cells, a hemoglobin concentration of 13 Gm. and 18,500 white blood cells with 82 per cent polymorphonuclear cells, 16 per cent lymphocytes and 2 per cent eosinophils; the urine gave a 4 plus reaction for albumin and showed occasional white blood cells. No new purpuric spots were noted and the physical condition remained excellent. By the end of two days, many of the smaller spots had faded considerably and no new lesions were observed. On the fourth day, laboratory reports were: 5,400,000 red blood cells, a hemoglobin concentration of 17 Gm. and 819,000 thrombocytes. The infant continued to gain weight, took his feedings well and showed no further evidences of bleeding into the skin or mucous membranes. The infant was discharged on December 8, weighing 4,450 Gm. and with the following laboratory data: The blood showed 4,500,000 red blood cells, a hemoglobin concentration of 14 Gm. and 637,000 thrombocytes, with normal results on urinalysis.

On the second day post partum, a study of the mother's blood showed 3,590,000 red blood cells, a hemoglobin concentration of 11 Gm., 1,127,000 thrombocytes and 12,000 white blood cells, with 80 per cent polymorphonuclear cells, 16 per cent lymphocytes and 4 per cent eosinophils. The blood was Rh positive. The infant has shown no further evidence of bleeding to the present.

In 1946, the mother again became pregnant. During this pregnancy she had no renal symptoms, the blood pressure remained normal and the course was uncomplicated. She was admitted at term on Feb. 21, 1947, in labor. She was given 2 mg. of vitamin K orally. After a seven hour labor, the membranes ruptured and she was delivered spontaneously. There was a moderate loss of blood during delivery, estimated at 100 cc. The infant, a boy, weighed 4,500 Gm. and had a strong cry and good color. Within two hours the baby was noted to have a generalized petechial hemorrhagic rash most prominent over the face, scalp,

shoulders and extremities. A few hemorrhages were present on the palatal surfaces. There was no bleeding from the stump of the umbilical cord. The anterior fontanel was soft. The scleras and conjunctivas were clear. The lungs were clear and the heart sounds strong and no murmurs were heard.

The spleen was not palpable and the edge of the liver was at the costal margin. The tourniquet test gave a positive reaction. Vitamin K (4.8 mg.) was given. The laboratory findings forty-eight hours after birth were as follows: red blood cells, 4,450,000; hemoglobin concentration, 13 Gm., and white blood cells, 10,600, with 78 per cent polymorphonuclear leukocytes and 22 per cent lymphocytes. Bleeding time was 1 minute and clotting time, 2 minutes 10 seconds. Thrombocytes numbered 380,000. The blood was Rh positive, and the Mazzini test gave a negative reaction. Results of urinalysis were normal. Culture of the blood was sterile. Clot retraction began in 45 minutes and was complete in 3 hours.

The infant progressed favorably and no new hemorrhagic lesions were noted. On February 26, the thrombocyte count was 471,000. On March 4, the skin was clear and the physical findings normal. Results of a follow-up examination on May 1 were again negative and the course of development had been normal. The thrombocytes then numbered 786,000. The subsequent history of the mother has been uneventful.

CASE 3.—R. C., a 27 year old Italian woman, was admitted to the hospital in active labor, at term, on March 20, 1946.

There had been two previous pregnancies in 1940 and 1943 with normal courses. Normal male infants, weighing 2,450 and 2,950 Gm., respectively, were delivered and their subsequent development to the present has been normal. The woman's past history was noncontributory. The family history was negative for purpura or bleeding tendencies.

The only unusual details pertaining to the present pregnancy were as follows: Morning nausea persisted throughout the pregnancy; she gained weight unduly (35 pounds [15.9 Kg.]), and with the onset of pregnancy she lost all appetite for milk, drinking only that amount necessary to color her coffee. Previously, she had always drunk an adequate amount of milk. On her admission her blood pressure was 150 systolic and 100 diastolic. No prelabor medication was used. Vitamin K (4.8 mg.) was administered during labor, and anesthesia was induced during the second stage with administration of a mixture of nitrous oxide and oxygen. On rupture of the membranes, the amniotic fluid was noted to be pale yellow. After a sixteen hour labor, a female infant, weighing 2,270 Gm., was spontaneously delivered.

The infant had an immediate, high-pitched cry, was active and had good color. She was transferred to the nursery for premature infants. Vitamin K (4.8 mg.) was given at this time. Two hours after birth many pinpoint-sized petechiae were seen on the scalp, face and neck. There were numerous petechial hemorrhages on the hard palate. The scleras were clear and a small amount of dried blood-tinged material was seen in the nares, but no active bleeding was observed. The anterior fontanel was soft. The lungs were clear; the heart sounds were strong, and no murmurs were heard. The abdomen was soft; the edge of the liver was at the costal margin, and the tip of the spleen was palpable just below the costal margin. No bleeding was observed from the umbilical stump.

At the end of eighteen hours, there were great numbers of petechiae scattered over the body and extremities, with several ecchymotic areas, measuring 1 to 3 cm. in diameter, over the back and buttocks. The color was fairly good;

a slight pallor of the lips and a mild degree of circumoral cyanosis were present. The infant's cry was now more highly pitched, with a slight inspiratory crow. She was still active and vigorous. The Rumpel-Leede phenomenon was present. A transfusion of 45 cc. of whole fresh blood (type O, Rh positive) was given without reaction. During the first day of life the following laboratory data were obtained before transfusion: Red blood cells numbered 3,700,000; the hemoglobin concentration was 12 Gm. Bleeding time was 2 minutes and clotting time, 4½ minutes. The blood was Rh positive. There were present 66,000 thrombocytes and 6,900 white blood cells, with 69 per cent polymorphonuclear leukocytes, 28 per cent lymphocytes, 5 per cent monocytes, 5 per cent normoblasts and 8 per cent nucleated red blood cells. The blood was of type O; the Mazzini reaction was negative and the blood culture, sterile.

On the second day, the child's color was poor and the cry weak. On the second and third days of life small numbers of new petechiae were discovered and the stool showed the presence of blood. A second transfusion of 45 cc. of whole fresh blood was given on the third day. On the fifth day, laboratory studies showed 4,200,000 red blood cells, a hemoglobin concentration of 13.5 Gm. and 84,000 thrombocytes. No new petechiae were noted and those present were fading rapidly. The baby appeared to be progressing satisfactorily. On the ninth day the thrombocyte count was 63,900 and the stool gave a faintly positive reaction for blood. On the twelfth day, the thrombocytes numbered 124,700, and the stools were free of blood. On the fifteenth day, the laboratory reported 3,630,000 red blood cells and a hemoglobin concentration of 11 Gm. The bleeding time was 2 minutes, and the thrombocytes numbered 130,700. The reaction to the tourniquet test was strongly positive. On her discharge from the hospital the baby had regained her weight at birth and was vigorous; a few fading petechiae were on the hard palate as the only evidence of the disease.

Post partum, the mother's blood pressure quickly returned to normal, 124 systolic and 80 diastolic. On the third day her laboratory data were obtained as follows: The bleeding time was 5 minutes, the clotting time, 6 minutes and the clot retraction time, normal. There were 520,000 thrombocytes; blood calcium measured 10.3 mg. per hundred cubic centimeters, and the blood was Rh positive.

Case 4.—R. J., a 31 year old American woman, was admitted to the hospital in active labor, at term, on April 22, 1946.

One previous pregnancy in 1942 had been normal and the child's development to the present was uneventful. The maternal past history revealed that she had always had epistaxis and bruised easily. The epistaxis was never profuse or frequent, and it had gradually decreased in frequency with age and did not occur at all during the first year of marriage. After the first delivery in 1942, the attacks of nosebleed began to appear at infrequent intervals. Occasional ulorrhea had occurred for many years. The family history revealed that her mother and four of her mother's sisters had a history of bruising easily. The mother had a severe hemorrhage with her last child and became extremely exsanguinated.

With the onset of the present pregnancy, the patient noticed that the ulorrhea increased in frequency, occurring daily. The attacks of epistaxis became much more frequent during the seventh month of this pregnancy, taking place about once a week and continuing up to the time of her confinement. During this pregnancy she gained 35 pounds in weight.

On her admission, no prelabor medication had been given. During the labor, meperidine (demerol®) hydrochloride U. S. P. (100 mg.) and vitamin K (4.8 mg.) were administered. Anesthesia was induced during the second stage with the use

of a mixture of nitrous oxide and oxygen. After a labor of twelve hours, a female infant, weighing 3,510 Gm., was spontaneously delivered without difficulty. One loop of the cord was hung loosely about the neck.

The infant breathed immediately, appeared quite active and had a lusty cry. No cutaneous lesions were observed at delivery. Four hours after birth prominent petechiae were noted on the body. On examination, the mucous membranes and skin showed good color, with a slight icteric tint present on the upper part of the face. Numerous petechiae were observed on the scalp, groins, popliteal areas and shoulders, with discrete petechial spots scattered over the trunk and extremities. There were ecchymotic areas over the shoulders, especially the right, and on the ankles, lower legs, upper arms and along the left anterior abdominal wall. The anterior fontanel was soft. The nares were clear. The scleras were clear with no evidence of icterus. Several petechial areas were seen on the right side of the hard palate. The lungs and heart were normal. The spleen was not palpable and the edge of the liver was at the costal margin. There was no oozing from the cord, but a small fresh hemorrhage was at the base of the cord. The genitalia were normal.

Within a few hours after birth the laboratory studies revealed 4,850,000 red blood cells and a hemoglobin concentration of 16 Gm. The bleeding time was 5 minutes and the clotting time, 3 minutes, with no clot retraction. The thrombocytes numbered 47,500. The tourniquet test had a negative reaction. The blood was Rh positive, and its type, O. The Mazzini test gave a negative reaction and the blood culture was sterile.

The number of petechiae increased greatly during the first twenty-four hours and the lesions on the palate were more pronounced. The icterus of the skin was more conspicuous, but the scleras were clear. A transfusion of 70 cc. of citrated fresh plasma from the father and from a group A compatible donor was given the infant twelve hours after birth.

On the second day the baby appeared quite well, and the laboratory data revealed 3,840,000 red blood cells, a hemoglobin concentration of 12 Gm. and 23,400 thrombocytes. A transfusion of 20 cc. of fresh whole blood was given on this day. On the third day the child had mild diarrhea which responded promptly to treatment. At this time the laboratory report revealed 11,700 white blood cells, with 73 per cent polymorphonuclear leukocytes, 22 per cent lymphocytes, 3 per cent monocytes and 2 per cent eosinophils. There were 35,000 thrombocytes, and the tourniquet reaction was negative. Another transfusion of 30 cc. of fresh citrated blood was given without reaction. On the fourth day, laboratory data showed 3,480,000 red blood cells. The bleeding time was 3 minutes and the clotting time, 4 minutes. There were 21,500 thrombocytes and 6,500 white blood cells, with 65 per cent polymorphonuclear leukocytes and 35 per cent lymphocytes. Results of urinalysis were normal, and tests of the stool showed occult blood. At four weeks the thrombocytes numbered 26,100; bleeding time was 10 minutes and clotting time, 2½ minutes. The tourniquet test gave a strongly positive reaction, and there were 3,270,000 red blood cells. A few petechial lesions were still present on the palate. At nine weeks the thrombocytes numbered 85,200 and the red blood cells, 3,500,000; bleeding time was 2½ minutes and clotting time, 3 minutes. There was no retraction of the clot. Clinically, the infant appeared vigorous and well. At 1 year of age, the thrombocytes numbered 899,000. The subsequent course of the child's development has been normal in every respect.

On the second day post partum a study of the mother's blood showed 3,010,000 red blood cells, a hemoglobin concentration of 9.5 Gm., 15,100 white blood cells, with 78 per cent polymorphonuclear leukocytes and 22 per cent lymphocytes, and 150,500 thrombocytes; bleeding time was 1 minute and clotting time, 4½ minutes, with normal clot retraction. The prothrombin time was 100 per cent of normal. Her blood was Rh positive. The Mazzini reaction was negative and the reaction to the tourniquet test, positive.

CASE 5.—M. C., a 27 year old Irish woman, was admitted to the hospital on Jan. 24, 1947, at term, in active labor. One previous pregnancy in 1943 had been normal. The past history was negative, and the family history was negative for purpura or bleeding tendencies.

No prenatal care had been given during the present pregnancy, and on her admission to the hospital there was no history of illness or bleeding during the pregnancy. The membranes had ruptured two hours before her arrival at the hospital, at which time labor had begun. The blood pressure was 148 systolic and 90 diastolic. Vitamin K (2 mg.) was administered; labor progressed in normal fashion, and anesthesia was induced during the second stage with the use of a mixture of nitrous oxide and oxygen. A male infant was delivered spontaneously one hour after the mother's admission.

The baby cried immediately and was active and vigorous. At birth, multiple small cutaneous hemorrhages were noted over the face, scalp, upper part of the chest and extremities, with a few similar lesions over the back and abdomen. These lesions did not fade on pressure. No lesions were noted in the mouth. The scleras were clear. There was no bleeding from the umbilical cord. The spleen was not palpable. The heart sounds were strong and the lungs clear. The anterior fontanel was soft. The Rumpel-Leede phenomenon was present.

At the end of eighteen hours, there were no new cutaneous lesions, although the existing ones were still prominent and numerous. The cry was strong and the infant was in good condition. The laboratory data at this time were as follows: Red blood cells were 5,400,000 and white blood cells, 28,600, with 94 per cent polymorphonuclear leukocytes and 6 per cent lymphocytes. The hemoglobin concentration was 17 Gm. The bleeding time was 2 minutes and clotting time, 4 minutes. There were 183,600 thrombocytes. The Mazzini test gave a negative reaction. The blood was Rh negative and the culture, sterile.

At forty-eight hours the baby's condition was good; the cutaneous lesions were fading, and a slight icterus was present. The baby's course continued favorably, and on the eighth day the red blood cell count was 4,775,000, the hemoglobin concentration, 14.5 Gm. and the thrombocytes, 808,000. At the age of 3 months, the baby was apparently well and there had been no further manifestations of the disease.

CASE 6.—R. J. was admitted to the hospital in active labor at term, on March 25, 1948. The past history and previous pregnancy were described under case 4. From the beginning of the fourth month of the present pregnancy, vitamin K had been administered daily orally, in doses of 2 mg.

With the exception of a mild ulorrhea, there had been no evidence of bleeding during the pregnancy. On her admission, in labor, 2 mg. of vitamin K was given, and during labor 100 mg. of meperidine hydrochloride U. S. P. was administered. Eight hours after her admission to the hospital, the membranes ruptured spontaneously, and ten minutes later the infant was delivered. The maternal loss of blood was slight.

The infant weighed 3,430 Gm. at birth and was a girl. The cry was immediate, the breathing normal and the color good. Shortly after her admission to the nursery, generalized cutaneous purpuric areas were observed. These lesions were confined chiefly to ankles and feet, groin and lower portion of the abdomen, both axillas and shoulders and the upper part of the back, with scattered lesions on the

TABLE

							Infant			
							Purpura			
Case No.	Author	Year	Sex	Born at Term or Premature	Weight at Birth, Gm.	Outcome	Skin	Other	Rumple-Leede Phenomenon	Hematuria
1	Dohrn [4]	1878	F	T	2,370	Lived	+	+	..	..
2	Glenn [6]	1893	..	P	2,045	Died	+	+	..	..
3	Zangemeister [7]	1898	..	T	.....	Died	—	+	..	..
4	Diehl [8]	1899	..	P	.....	Died	+	+	..	..
5	Mosher [25]	1923	F	T	2,950	Died	+	—	..	..
6	Waltner [27]	1924	F	P	1,800	Lived	+	—	..	..
7	Leschke and Wittkower [28]	1925	M	T	3,150	Lived	+	+	..	+
8	Liebling [26]	1926	F	T	4,000	Lived	+	+	..	+
9	Rodecurt [30]	1928	F	T	2,830	Lived	+	+	..	—
10	Greenwald and Sherman [12]	1929	M	T	.....	Died	+	+	+	—
11	Bayer [20] I	1931	F	T	2,700	Lived	+	—	+	..
12	Bayer [20] II	1931	F	P	2,000	Lived	+	—	+	..
13	Guttfreund [23]	1932	F	T	3,100	Lived	+	+	..	—
14	Sanford and others [22]	1936	F	T	3,608	Lived	+	+	..	—
15	Posner [29]	1937	F	T	4,400	Lived	+	+	..	..
16	Davidson [15]	1937	F	T	3,470	Lived	+	+	+	—
17	Urbanski and Hutner [16] I	1942	F	T	3,540	Lived	+	+	..	..
18	Urbanski and Hutner [16] II	1942	M	T	3,175	Died	+	+	..	..
19	Whitney and Barritt [17] I	1942	M	T	2,849	Died	+	+	..	..
20	Whitney and Barritt [17] II	1942	M	P	2,424	Died	+	+	..	..
21	Finn [18] I	1944	..	T	3,100	Died	+	+	..	..
22	Finn [18] II	1944	..	T	3,300	Lived	+	—	..	..
23	Morrison and Samwick [31]	1945	M	T	2,948	Lived	+	+	..	..
24	Schefrin and Sheehtman [1]	1945	F	T	1,984	Lived	+	+	..	..
25	Patterson [24]	1946	M	T	3,580	Lived	+	+	..	..
26	Waters [2]	1946	M	T	4,880	Lived	+	+	+	—
27	Goldstein [4]	1947	M	T	2,682	Lived	+	—	..	..
28	Talmadge and Berman [19] I	1947	F	T	.....	Lived	+	+	..	..
29	Talmadge and Berman [19] II	1947	F	T	.....	Lived	+	+	..	..
30	Talmadge and Berman [19] III	1947	F	T	.....	Lived	+	+	..	..
31	McAlenney and Kristan I	1947	M	T	4,580	Lived	+	+	+	—
32	McAlenney and Kristan II	1947	M	T	4,500	Lived	+	+	+	—
33	McAlenney and Kristan III	1947	F	T	2,270	Lived	+	+	+	—
34	McAlenney and Kristan IV	1947	F	T	3,510	Lived	+	+	—	—
35	McAlenney and Kristan V	1947	M	T	3,560	Lived	+	—	+	—
36	McAlenney and Kristan VI	1948	F	T	3,430	Lived	+	+	+	—

arms, wrists and lower part of the face. There were a few small hemorrhages over the surface of the hard palate. The lesions varied from pinpoint to a few areas 1 cm. in diameter. The anterior fontanel was soft and the conjunctivas clear. The heart and lungs were normal. The spleen was not palpable. The tourniquet reaction was positive. The laboratory data obtained at the end of twenty-four hours revealed a hemoglobin concentration of 14 Gm., 4,600,000 red blood cells

and 23,900 white blood cells, with 76 per cent polymorphonuclear cells. The bleeding time was 1 minute and the clotting time, 3½ minutes, with slight clot retraction in 24 hours; thrombocytes numbered 35,000. The prothrombin test showed no coagulation in 60 seconds. The reaction to the Mazzini test was negative. The blood culture was sterile and the blood was Rh positive.

ary of Cases

Therapy												Mother							
Blood Transfusion	Other	Thrombocytes, Thousands	Bleeding Time, Min.	Clotting Time, Min.	Prothrombin Time, % of Normal	Clot Retraction	Rh Factor	Red Cell Count, Millions	Hemoglobin Concentration	White Cell Count, Thousands	Blood Culture	Serologic Reaction, Syphilis	Age, Years	Parity	Rh Factor	Outcome	Purpura: During Pregnancy	Purpura: Past History	Purpura: Family History	Splenectomy
..	..	....	..	..	..	..	..	...	.....	....	..	..	41	2	..	Lived	+	..	..	..
..	..	....	..	..	..	..	..	...	.....	....	..	..	22	1	..	Lived	+	—	..	..
..	..	....	..	..	..	..	..	...	.....	....	..	..	25	1	..	Lived	+	—	—	..
..	..	....	..	..	..	..	..	...	.....	....	..	..	36	6	..	Died	+	—	—	..
..	..	....	..	..	..	..	..	...	.....	....	..	..	..	6	..	Lived	+	..	..	..
..	..	90	12	10	..	—	..	5.6	100%	8.1	..	..	38	1	..	Lived	+	+	..	..
+	..	Few	12	3	..	Poor	..	6.0	136%	17.8	..	—	28	7	..	Lived	+	+	—	..
..	+	40	Normal	Normal	..	..	..	6.0	110%	....	..	..	22	1	..	Lived	+	—	—	..
..	..	127	6+ hr.	6	..	Poor	..	5.7	120%	20.0	—	..	21	2	..	Lived	—	—	—	..
..	..	30	5	35	..	—	..	6.1	122%	12.0	..	—	..	..	—	Lived	..	..	..	..
..	..	50	40	18	..	..	..	...	.....	....	..	..	..	..	..	Lived	..	..	..	..
..	..	48	6½	5½	..	..	..	...	.....	....	..	..	..	..	..	Lived	..	..	..	..
+	..	—	40	6	..	Poor	..	1.8	62%	16.0	..	—	18	..	..	Lived	—	—	+	..
..	..	20	..	..	..	..	..	5.8	110%	16.0	..	..	22	1	..	Lived	+	+	+	—
+	..	10	25	2	..	..	..	2.9	60%	24.5	..	..	28	2	..	Lived	+	+	..	—
+	+	56	3	7	..	—	..	5.1	24 Gm.	42.7	..	..	21	1	..	Lived	+	+	..	+
+	..	60.8	4½	2	..	..	..	5.6	85%	....	..	..	32	2	..	Lived	..	+	—	+
..	..	....	..	..	..	..	..	...	.....	....	..	..	25	1	..	Lived	+	+	—	—
+	..	80	1	3½	..	..	..	...	.....	....	..	..	26	1	..	Lived	+	+	..	+
+	+	90	11	1½	..	..	..	5.5	100%	12.9	..	..	28	2	..	Lived	+	+	..	+
+	..	120	7	3	..	..	..	5.4	.....	....	..	..	23	1	..	Lived	+	+	..	+
+	..	40	90	..	..	—	..	...	.....	....	..	..	26	3	..	Lived	—	+	..	+
..	..	40	7	3½	..	—	..	4.0	81%	15.5	..	..	..	1	..	Lived	..	+	+	..
+	..	67.2	2	4	..	Normal	..	4.2	114%	19.0	..	..	..	..	+	Lived	—	—	—	—
+	+	18.5	4	6	..	..	..	6.2	118%	....	..	—	22	1	+	Lived	+	+	+	—
+	+	21.8	1½	4	47	1+	+	4.6	17 Gm.	19.0	—	..	34	8	+	Lived	—	—	+	—
—	+	63	1½	4	..	..	+	3.2	8 Gm.	12.0	..	..	..	..	+	Lived	..	..	..	..
+	..	85	30	..	..	..	..	4.2	.....	....	..	..	20	1	..	Lived	+	+	..	+
+	..	50	41	15	..	—	..	5.1	.....	....	..	..	24	2	..	Lived	—	+	..	+
+	..	—	62	3	..	—	..	3.5	.....	....	..	..	25	3	..	Lived	+	+	..	+
—	+	65.7	5	5	Normal	8 hr.	+	4.3	14 Gm.	18.5	—	—	24	5	+	Lived	—	+	—	—
—	+	380	1	2	..	3 hr.	+	4.4	13 Gm.	10.6	—	—	26	6	+	Lived	—	+	—	—
+	+	66	2	4½	..	..	+	3.7	12 Gm.	6.9	—	—	27	3	+	Lived	—	—	—	—
+	+	47	5	3	Normal	—	+	4.8	16 Gm.	11.7	—	—	31	2	+	Lived	+	+	+	—
—	+	183	2	4¼	..	..	+	5.4	17 Gm.	23.6	—	—	27	2	+	Lived	—	—	—	—
—	—	35	1	3½	— in 60 sec.	Slight in 24 hr.	+	4.6	14 Gm.	23.9	—	—	32	3	+	Lived	—	+	+	—

Vitamin K was not administered to the infant after birth. The condition of the baby remained good, and no new petechiae were noted during the first forty-eight hours of life. At the end of forty-eight hours, the thrombocytes numbered 400,000, and the hemoglobin concentration was 13.5 Gm. During the next two days, there was gradual fading of the petechial lesions and on the fifth day of life, the laboratory data were: prothrombin time, 15.5 seconds (96 per cent of

normal); red blood cells, 4,500,000; hemoglobin concentration, 14 Gm.; white blood cells, 9,050, with 75 per cent polymorphonuclear cells, 24 per cent lymphocytes and 1 per cent eosinophils. Thrombocytes numbered 400,000. The reaction to the tourniquet test was negative on this day.

The infant was discharged from the hospital with the mother on the sixth day of life. There had been no hematuria, hematemesis or melena observed during the course in the hospital.

On the first postpartum day, the mother's blood showed a hemoglobin concentration of 70 per cent. The Mazzini reaction was negative. The blood was Rh positive and the tourniquet reaction was negative.

The subsequent course of the infant's development had been uneventfully normal.

COMMENT

There have been 28 published reports on the subject of purpura in the newborn period, and they cover 34 cases. The cases of Glenn,[6] Diehl,[8] Leschke and Wittkower,[28] Rodecurt,[30] Bayer [20] and Guttfreund [22] have not been mentioned in previous reviews. The largest group of cases analyzed from a statistical point of view is contained in the report of Waters,[2] who reviewed 17 cases in 1946. In the present study, the cases of Hanot and Luzet,[5] Rushmore,[9] Conti [13] and Siegler [14] have been omitted for reasons previously mentioned. Goldstein [21] did not mention the case of twins reported by Bayer,[20] in 1931. In the case of these sets of twins it is interesting to note that, while all 4 infants had thrombopenia, only 1 of each pair had cutaneous evidence of purpura. This occurred in the infants with the more significantly altered laboratory data, including lower thrombocyte counts. Unfortunately, in the unusual case reported by Greenwald and Sherman,[12] no studies were made of the mother in an effort to detect familial thrombopenia. We have included in our series 1 case in which the thrombocyte count was only slightly diminished. In this case (case 2) there was a maternal past history of bleeding, and the previous pregnancy had resulted in a purpuric infant with thrombopenia. In the present instance, the child, with the exception of severe thrombopenia, revealed an identical clinical picture. On this basis the diagnosis appears valid.

This analysis includes 30 of the cases previously reported, with the addition of the 6 new cases. The sex distribution shows 19 girls, 12 boys and 5 whose sex was not mentioned. Of the 36 infants, 27 lived and 9 died, representing a general mortality rate of 25 per cent. In the cases in which the sex was reported, the female infants fared better, since 18 of the 19 lived, whereas only 8 of the 12 male infants survived. As more cases are reported, the mortality rate appears lower than has been indicated by previous figures. There were 30 infants born at term and 6 premature infants. All the latter had weights at birth under 2,500 Gm., and 3 died.

The most constant physical sign of the disease is the appearance of cutaneous purpuric lesions, present at birth or shortly thereafter. These were noted in 35 of the infants. Gastrointestinal hemorrhage has been commoner than genitourinary, melena being reported in 13 cases and hematuria in only 2. Splenomegaly is not a sign of this disease and has not been reported in any case. The reaction to the tourniquet test was mentioned as being positive in 10 cases and negative in 1 case and was unmentioned in the remainder. Thus, when performed, it has had a predominantly positive reaction.

The thrombocytes were consistently reduced. Although the normal thrombocyte count varies widely with different methods, and is normally subject to unusual fluctuations, the count was below 100,000 in 25 of the 29 cases in which an estimation had been made. That the diminished thrombocyte level does not forecast a fatal prognosis is suggested by the observation that 22 of the 25 infants with thrombocyte counts below 100,000 survived.

TABLE 2.—*Effect of Purpura in Mother on Infant*

	Results in Infants									Total	
							No Sex Mentioned				
Condition of Mother	Male	Lived	Died	Female	Lived	Died		Lived	Died	Lived	Died
Maternal history negative for purpura during pregnancy	7	6	1	9	9	0	1	1	0	16	1
Purpura in past history with no purpura during pregnancy	3	3	0	3	3	0	1	1	0	7	0
Purpura in mother during pregnancy	5	2	3	10	9	1	4	0	4	11	8
Purpura in maternal past history and during pregnancy	5	2	3	7	7	0	1	0	1	9	4
Purpura in maternal past history	8	5	3	8	8	0	2	1	1	14	4

The average bleeding time was 14½ minutes and the average clotting time was 7 minutes. These values show a tremendous variation in individual cases and many different methods have been used in their determination. It would be extremely difficult to exclude or include certain cases from this classification on the basis of the values for bleeding or clotting times. In the cases in which it was studied, normal syneresis seldom occurred. The red blood cell count was over 4,000,000 in 21 of the 26 cases in which estimations were reported.

The appearance of purpuric disease in the mother during pregnancy is of prognostic significance. In 19 of the 36 mothers, purpura appeared during pregnancy, with an infant mortality rate of 42 per cent, whereas in the 17 mothers who did not exhibit purpura during pregnancy, the infant mortality rate was 6 per cent. There were 7 mothers with a past history of purpura and no evidence of the disease during their pregnancy. All 7 of the infants in this group survived. Thus, it would appear that purpura during pregnancy is accompanied with a greatly reduced chance of survival in the infant. Of the 19 mothers in whom purpura developed during pregnancy, only 1 mother died.

Burnett and Klass [33] have written an excellent and lucid paper discussing and classifying some of the reported cases from an obstetric point of view.

The administration of vitamin K as a prophylactic measure to any infant born to a mother with suggestive purpuric disease is strongly advised. This procedure should be carried out regardless of the infant's condition at birth, since the purpuric manifestations may not appear immedately at birth. Blood transfusions seem to be of value only in correcting any anemia which might develop, since it is impossible to demonstrate any definite effect in altering the final outcome. Of the 36 infants, 17 were given blood. Of the group who were given blood, 3 died, and these infants showed evidence of visceral bleeding alone or with intracranial bleeding. Of the group of 19 infants who did not receive blood, 6 died, and of these 3 were dead at birth, 2 died at ten and thirty-six hours, respectively, after birth, and 1 [12] died shortly after admission to the hospital, on the fourteenth day of life.

The cause of the purpura in the offspring in the reported cases had been attributed to any one or a combination of the following factors: thrombopenia; quantitative and qualitative thrombocytic defects; a pathologic destruction of thrombocytes in the spleen; failure of thrombocyte production by the megakaryocytes in the bone marrow; decreased blood calcium; diminished vitamin C concentration; increased capillary fragility; absorption of toxic substances from the maternal blood and, uninformatively, merely a transitory hemorrhagic diathesis. The interesting comments of Sanford and his associates [23] to the effect that qualitative rather than quantitative changes in the thrombocytes, a familial condition, may play a more important etiologic role than generally assumed may be pertinent. The cases with a familial history of hemorrhagic diathesis may form a link, as Krömeke [34] hypothecated, between essential thrombopenia and the so-called thrombasthenia and may point to a common etiologic factor which is not merely concerned with the numerical reduction of thrombocytes. Krömeke's familial cases showed thrombocyte counts varying from normal to 28,000. Glanzmann [35] noted 8 families with a bisexual history of purpura, nonsolidifying clots and a normal thrombocyte count. He termed this

33. Burnett, C., and Klass, I.: A Review of the Problem of Purpura During Pregnancy, J. Obst. & Gynec. Brit. Emp. **50**:393, 1943.

34. Krömeke, F.: Zur Frage der hereditären hæmorrhagischen Diathese (Thrombasthenie), Deutsche med. Wchnschr. **48**:1102, 1922.

35. Glanzmann, E.: Hereditäre hämorrhagische Thrombasthenie, Jahrb. f. Kinderh. **88**:1, 1918.

condition hereditary hemorrhagic thrombasthenia. Grulee and Sanford [36] mention 1 possibly similar case and speculate that such families as Glanzmann's may exist. Duke's case [37] is similar. As Sanford remarked, perhaps various types of purpura hemorrhagica are more or less severe degrees of this condition occurring in persons with a common constitutional anomaly. Quick,[38] in referring to the cases of Davidson, Sanford and Waltner, commented on the likelihood that a toxic factor from the mother was responsible. As more careful studies are continued, the picture undoubtedly will lose much of its present confusion.

The criteria proposed by Morrison and Samwick [31] for a diagnosis of thrombopenic purpura would, if considered, result in the nullification of almost all reported cases. The diagnosis of this disease should be considered in all cases of hemorrhage, cutaneous or other, occurring during the newborn period. In arriving at a possible diagnosis, one must attempt to rule out the possible presence of sepsis, syphilis, erythroblastosis fetalis, hemorrhagic disease of the newborn, other hereditary hemorrhagic diatheses and the rare toxoplasmosis.[39]

SUMMARY

We have presented a complete review of the literature on thrombopenic purpura, with a statistical study and the presentation of 6 new cases of the disease. The exact status of the disease has been vague and incompletely understood. Thirty-six reported cases have been studied and subjected to statistical analysis. On two occasions the disease has been described in twins. There have been 5 cases reported in which splenectomy had previously been performed on the mother. The general mortality rate has been found to be 25 per cent, with female infants surviving oftener than male. About 80 per cent of the infants were born at term. The characteristic picture of the disease shows (1) a generalized purpuric eruption appearing at, or shortly after birth; (2) occasional melena; (3) absence of splenomegaly; (4) usually positive

36. Grulee, C. G., and Sanford, H. N.: The Newborn, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1945, vol. 1, chap. 42, p. 87.

37. Duke, W. W.: The Relation of Blood Platelets to Hemorrhagic Disease: Description of a Method for Determining the Bleeding Time and Coagulation Time and Report of Three Cases of Hemorrhagic Disease Relieved by Transfusion, J. A. M. A. **55**:1185 (Oct.) 1910; The Pathogenesis of Purpura Hemorrhagica, with Especial Reference to the Part Played by Blood-Platelets, Arch. Int. Med. **10**:445 (Nov.) 1912.

38. Quick, A. J.: The Hemorrhagic Diseases and the Physiology of Hemostasis, ed. 1, Springfield, Ill., Charles C Thomas, Publisher, 1942, p. 142.

39. Callahan, W. P.; Russell, W. O., and Smith, M. G.: Human Toxoplasmosis, Medicine **25**:343, 1946.

reaction to the tourniquet test, and (5) reduction in blood thrombocytes As a rule, no anemia is present except when hemorrhage has been severe. Bleeding and clotting studies may be helpful but are often inconclusive, and the results show a great variation. The occurrence of purpura in the mother during pregnancy in this series was accompanied by an infant death rate of 42 per cent; the absence of purpura during pregnancy was accompanied by an infant mortality rate of 6 per cent. For this reason the prophylactic use of vitamin K is advised for infants born to mothers with suggestive purpuric disease, regardless of the infant's condition at birth. Blood transfusions are of value only in correcting anemia from hemorrhage. The disease appears to be benign and self limited in most instances. There have been many interesting hypotheses offered to explain the disease. The diagnosis should be considered in all cases of hemorrhage during the newborn period. One must rule out the possibility of septicemia, syphilis, erythroblastosis, hemorrhagic disease of the newborn, other hereditary hemorrhagic diatheses and toxoplasmosis.

CONCLUSIONS

Thrombopenic purpura of the newborn occurs infrequently. The disease appears to be benign and self limited in most instances. The occurrence of purpura during pregnancy is associated with an unfavorable prognosis in the infant. The administration of vitamin K as a prophylactic measure to an infant born to a mother with suggestive purpuric disease is advised. A more complete study of cases in the future will further clarify existent confusion regarding the classification and diagnostic criteria.

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ARACHNODACTYLY

Review of Recent Literature and Report of a Case with Cleft Palate

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SINCE Marfan's original report in 1896,[1] approximately 325 cases of arachnodactyly have been recorded in the literature. In addition to the presence of long, thin, "spider-like" digits, various other anomalies, especially of the eye, skeleton, cardiovascular system and external ear, have been described in patients with this condition. Rados,[2] in 1942, summarized the distinctive malformations in 204 previously recorded cases. His data showed that about 15 per cent of the patients had been reported to have a high palate, but only 2 patients, those of Piper and Irvine-Jones [3] and Zuber,[4] had had a cleft palate. I found no additional case of arachnodactyly with cleft palate reported, although Dax (1940) [5] described a patient with arachnodactyly who had 2 siblings with cleft palates. The infrequency of the occurrence of the combination prompts me to record the following case.

REPORT OF CASE

A 6 week old baby girl was admitted to the Babies' Hospital, of Wilmington, N. C., to the private service of Dr. J. Buren Sidbury, on April 11, 1948, with pyelonephritis and bronchitis, which were successfully treated with sulfadiazine and streptomycin.

History.—The baby was born after a full term, uncomplicated pregnancy and normal delivery; her weight at birth was 8 pounds ¾ ounce (3,650 Gm.). The parents and three siblings were living and well. There was no consanguinity between the parents and no knowledge of any congenital anomalies in the family.

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1. Marfan, M. A.: Bull. et mém. Soc. méd. d. hôp. de Paris **13**:220, 1896.

2. Rados, A.: Marfan's Syndrome (Arachnodactyly Coupled with Dislocation of Lens), Arch. Ophth. **27**:477 (March) 1942.

3. Piper, R. K., and Irvine-Jones, E.: Arachnodactylia and Its Association with Congenital Heart Disease: Report of Case and Review of Literature, Am. J. Dis. Child. **31**:832 (June) 1926.

4. Zuber, M. A.: Un cas de dolichosténomélie (arachnodactylíe), Bull. Soc. de pédiat. de Paris **25**:181, 1927.

5. Dax, E. C.: Retinitis Pigmentosa, Quart. J. Med. **9**:263, 1940.

Physical Examination.—The physical findings, other than those referable to the acute illness, noted on admission were as follows: The baby had an old, sad expression. The lower jaw was less prominent than is customary. The ears, especially the left one, were somewhat peaked. There was a 1 cm. hole in the hard palate in the midline. The eyes showed no abnormality on gross and funduscopic examination (Dr. David Sloan) but were difficult to examine. There was no gross skeletal deformity of the chest. The heart sounds were of good quality and the rhythm regular; no murmurs were heard. The baby had somewhat thin, extremely long fingers, which were frequently moved and hyperextended.

Photograph of patient showing long fingers, peaked ear and receding lower jaw.

The feet were also long and thin. The length of the arms and legs did not strike one as being out of proportion to the body.

Measurements.—The body length was 22 inches (55.9 cm.); the circumference of the head was 13⅜ inches (34 cm.), of the chest, 13 inches (33 cm.) and of the abdomen, 12⅛ inches (30.8 cm.). The length from shoulder to elbow was 4 inches (10.2 cm.); from elbow to wrist, 3 inches (7.6 cm.); from wrist to end of third finger, 2½ inches (6.4 cm.); from head to umbilicus, 10¾ inches (27.3 cm.); from the anterior superior iliac spine to the knee, 5 inches (12.7 cm.), and from the knee to the ankle, 5⅞ inches (14.9 cm.), while the foot was 3⅜ inches (8.6 cm.) long.

The baby had a negative Wassermann reaction. Her blood was type A, Rh positive.

REVIEW OF THE LITERATURE

A review of the anomalies of the patients described since Rados' summary was made and is recorded in table 1. Only subjects specifically described as having "spider digits" or said to have had arachnodactyly were included; no atypical cases were included. It should be noted that in some of the reported cases, although deformities were not stated to be present, their absence was not specifically mentioned. In such instances, there are dots in the appropriate spaces. When the sign was stated to be absent, a minus sign is used. Ectopia lentis was bilateral unless stated otherwise in the table. The presence of hypotonia, diminished muscle mass or atrophy did not necessarily reflect the physical strength of the patient. Some, but not necessarily all, ligaments were lax in patients showing this sign, and the corresponding joints were hyperextensible. Changes in the chest were described in the original articles as pigeon breast, funnel chest or flat chest. The facies were usually described as melancholic, old or doleful, occasionally as frightened, pained or indifferent. Patients were white unless otherwise described under "Miscellaneous."

The total number of patients showing abnormalities in each large category is listed at the end of table 1. In arriving at the figures for the totals, the following notations in the table were not considered as positive signs when any one was the only abnormality in the category: ocular changes: myopia, broad eye socket, closely set eyes, blinking, prominent eyes or exophthalmos; cardiovascular defects: systolic (apical) murmur, slight dilatation of all chambers on fluoroscopy, friction rub, extrasystoles, undescribed pathologic cardiac changes, extra sounds during systole or rheumatic heart disease; skeletal changes: microcephaly, fractures, slight skeletal changes, subluxation, trabeculation on roentgenogram, pes planus or high patella; familial disorders: tallness.

Table 2 shows the numbers of patients with various combinations of abnormalities. Each patient is tabulated under as many categories as his disorders fit; for example, a patient with ectopia lentis, aural and palatal abnormalities is recorded under each abnormality alone, under "ectopia lentis and aural changes," "aural and palatal changes," "ectopia lentis and palatal changes" and "ectopia lentis, aural and palatal changes."

COMMENT

In this series, three fourths of the 117 patients (56 males, 61 females) had pathologic ocular changes; the commonest forms were ectopia lentis and iridodonesis. Three fourths of the patients had some type of

Author	Age	Sex	Ocular Changes: Iridodonesis	Ocular Changes: Ectopia Lentis	Ocular Changes: Miscellaneous	Aural Changes	Cardiovascular Defects	Diminished Subcutaneous Fat Hypotonia	Atrophy, Diminished Muscle Mass	Lax Ligaments	Contractures
Paéz Allende, F.: An. argent. de oftal. **7**: 81, 1946; Rev. Asoc. méd. argent. **59**: 1313, 1945	7 yr.	F	+	+	Partial aniso-chromia of irises; myopia	.....	.....	+	+	+	Hammer toe
Baer, R. W.: Taussig, H. B., and Oppenheimer, E. H.: Bull. Johns Hopkins Hosp. **72**: 309, 1943	14 yr.	F	..	+	Prominent	.....	Auricular fibrillation; enlarged heart; patent foramen ovale; slit between auricles; fusiform aortic aneurysm	..	..	+	Hammer toe
	25 yr.	M	..	+	Myopia	.....	Rough presystolic murmur; patent foramen ovale; interauricular defect; fusiform aortic aneurysm; left subclavian and carotid arteries from one opening	..	..	..	Hammer toe
Barron, A. A.: North Carolina M. J. **3**: 353, 1942	16 yr.	M	..	+	.....	.....	To and fro apical friction rub	+	+	..	.....
Bean, W. B., and Fleming, J. G.: Ohio State M. J. **36**: 155, 1940	27 yr.	F	+	+	Right external strabismus	Normal	Harsh systolic murmur; systolic thrill	..	+	+	.....
Beauvieux; Bessière, and Pétriat: J. de méd. de Bordeaux **116**: 109, 1939	9 yr.	M	+	+	.....	Longer than normal	.. ..	..	..	+	.....
Bergstrand, C. G.: Acta pædiat. **30**: 345, 1943	2 days	F	..	..	No dilatator pupillae muscle present	.....	Normal	+	..	..	.....
Bietti, G.: Boll. d'ocul. **24**: 83, 1945	13½ yr.	F	..	..	Strabismus; bilateral exophthalmos; OD: subatrophic papilla, tortuous retinal vessels; OS: atrophic papilla	.....	....	..	..	..	.....
Boudet, G.; Balmès, J., and Barnay, J.: Bull. Soc. pédiat. de Paris **37**: 188, 1939	15 yr.	M	..	..	Blue scleras	Normal	Heart normal on examination, electrocardiogram and roentgenogram	..	..	..	.....
	14 yr.	M	..	..	Normal	.....	Heart normal	..	..	..	.....
Bhat, P. K.: Antiseptic **43**: 651, 1946	14 yr.	M	+	+	Small, eccentric pupils; bilateral megalocornea: right cataract; anterior chambers deep below	.....	.....	..	..	..	.....
Cassady, J. V., and McFarland, C. B.: Am. J. Ophth. **30**: 469, 1947; Tr. Indiana Acad. Ophth. & Otolaryng. **29**: 35, 1946	52 yr.	M	+	OS	Myopia; OD: yellow, band-shaped opacity of most of cornea, surface granular; glaucoma; OS: retinal detachment	.....	.....	+	+	..	.....
	38 yr.	M	+	+	.....	.....	.....	..	..	..	.....
Caussade, L., and Vérain, M.: Rev. méd. de Nancy **67**: 596, 1939	13½ yr.	F	..	..	Normal	.....	Dilated heart, displaced to right; congenital heart disease; no murmur	+	+	+	Clawed toes
Corcelle; Berthon, and Grèze, E.: Rev. d'oto-neuro-opht. **17**: 143, 1939	28 yr.	F	..	OD	OS: atrophic iris, lens not visible	.....	Heart normal	+	..	..	.....

Skeletal Changes												
Long												
Feet	Arms	Legs	Kyphosis	Scoliosis	Chest	Pes Planus	Dolichocephaly	High-arched Palate	Miscellaneous	Facies	Familial Disorders	Miscellaneous
+	..	..	..	..	..	..	..	+	Genu valgum; 3d and 4th fingers concave laterally	+	Parents and 3 sibs: normal; parents were first cousins	
..	..	..	..	+	..	+	..	..	.....	..	Paternal uncle: congenital heart disease	Postmortem examination
..	..	..	..	..	+	Left	..	+	Legs of uneven length; bilateral hallux valgus; slightly webbed fingers; defect of sacral arch; bilaterally dislocated clavicle	..	Father: tall, thin, long thin arms, poor eyes; paternal grandfather: tall, thin; parents: third cousins; one brother; normal	Negro; no rheumatic heart disease; sudden death, with postmortem examination
+	..	..	..	..	..	..	+	..	.. ..		Maternal grandfather and 4 sibs: arachnodactyly; mother and 4 of 9 sibs: arachnodactyly; 5 of 8 sibs: arachnodactyly; 4 sibs: ectopia lentis	Two attacks of lymphocytic choriomeningitis
..	..	..	+	+	+	..	+	+	Large sacral foramens; synostosis of distal part of left tibia and fibula	..	Maternal cousin and uncle: unknown type of congenital deformities; 7 mo. baby: deformed chest, right hip moderately spastic, head to left	Large retroperitoneal cyst with lining attached to sacral vertebrae and continuous with large foramen of 2d right sacral vertebra
+	..	..	..	..	..	..	+	..	Bilateral genu recurvatum	+	Father: ectopia, thin until 18 yr.; brother: thin, good vision	Inguinal hernia; osteomyelitis of right fibula; basal metabolic rate —24%
+	+	+	..	..	+	..	..	..	.....	..	Parents and 2 sibs: well	Postmortem examination: left lung: one lobe; increased eosinophils in pituitary; bronchopneumonia
..	..	..	..	..	..	..	..	+	.....	..	Mother: tortuous retinal vessels; father: myelinated fibers of papilla of left eye; brother: somewhat long thin digits	7 mo. pregnant; anosmia
+	..	..	+	..	..	..	+	..	Many fractures	..	Parents normal, no consanguinity	Webbed fingers
..	..	+	..	Slight	—	..	—	..	.....	..	Healthy family	Positive Meinicke reaction
+	..	..	..	..	..	..	..	..	.....	..	.....	Hindu
..	+	+	..	..	+	..	+	..	High patella; excess curvature of soles	+	Brother of next patient; mother: tall, thin, thick glasses; 4 normal sibs; sister: 55 yr. old, arachnodactyly, glaucoma after attempted extraction of cataract; brother: 45 yr. old, thin, long hands and feet, thick lenses	
..	..	..	..	..	..	..	..	..	High patella	+		
+	..	+	+	+	+	..	+	..	Atresia of lower jaw; genu valgum	+	Mother, father and sibs healthy	Rectal prolapse; sudden death
..	+	+	+	+	+	+	+	+	Tendency to genu valgum	..	Parents, sibs and 2 yr. old child healthy	

Author	Age	Sex	Ocular Changes: Iridodonesis	Ocular Changes: Ectopia Lentis	Ocular Changes: Miscellaneous	Aural Changes	Cardiovascular Defects	Diminished Subcutaneous Fat	Hypotonia, Atrophy, Diminished Muscle Mass	Lax Ligaments	Contrac
Couto, D.: Hospital, Rio de Janeiro **25**: 673, 1944	29 yr.	M	..	—	Marked exophthalmos; conjunctival hyperemia	.....	Heart normal	+	+	+	.....
Dahlerup, J. V.: Ugesk. f. læger **104**: 64, 1942	10 yr.	M	+	+	Bilateral buphthalmos; megalocornea; deep chambers; right divergent strabismus	.....	Systolic murmur and thrill in 2d and 3d interspaces; enlarged heart; possible patent ductus arteriosus	+	+	+	Hamm toe; fe ion of wrist right finger
Dax, E. C.: J. Ment. Sc. **87**: 434, 1941	17 yr.	F	..	—	Deep; some corectopia and megalocornea	Bilaterally pointed; right abnormal	Heart normal on physical examination; cyanosis	+	..	+	.....
Dax, ibid., and Dax,[5] 1940	27 yr.	M	..	..	Heterochromia; bilateral cataract; divergent strabismus; eccentric pupils; night blindness	Long, narrow; deaf	No enlargement of heart or murmur	..	..	—	.....
Dax, E. C.: Brit. J. Ophth. **25**: 24, 1941	18 yr.	F	..	..	Blind; corectopia; no pupillary reaction to light; slight divergent strabismus and vertical nystagmus; myopia	Small, adherent lobules	Systolic apical murmur	..	..	+	.....
Deutch, S. S.: Am. J. Ophth. **25**: 1102, 1942	14 yr.	M	OS	+	OD: shrunken, deviated globe; opaque cornea; shallow anterior chamber; OS: megalocornea, part of iris atrophic	.....	.....	+	..	..	1st an finger clawe
Dorrance, T. O.: J. Pediat. **31**: 679, 1947	7 yr.	M	+	..	Myopia, iris thin and devoid of pigment; lenses tremulous	.....	Heart normal	+	+	..	.....
Ehlertsen, C. F.: Nord. med. (Hospitalstid.) **3**: 2323, 1939	31 yr.	M	..	+	Unequal pupils; blue scleras	.....	Heart normal	+	+	..	Flexio 5th fi
Ellis, R. B.: Arch. Dis. Childhood **15**: 267, 1940	32 yr.	M	+	+	Practically blind since birth	Rather prominent	Heart normal	+	+	..	.....
	4 yr.	F	+	+	Pupils dilate poorly	.....	Enlarged heart; middiastolic apical murmur; systolic murmur in 3d and 4th interspaces, left of sternum	..	..	+	Hamm toe
Etter, L. E., and Glover, L. P.: J. A. M. A. **123**: 88 (Sept. 11) 1943	21 yr.	M	..	OS	Myopia; OS: congen'tal peripheral opacities	Protrusion of upper half	Aortic insufficiency; enlarged heart; chronic dissecting aneurysm of ascending aortic arch (ruptured)	..	+	+	.....
Fahey J. J.: Arch. Surg. **39**: 741 (Nov.) 1939	5½ yr.	M	+	..	Myopia	Large	.....	+	+	+	.....
	25 mo.	F	+	+	Unequal pupils, not dilating on left; megalocornea; hydrophthalmos; shallow anterior chamber	.....	.....	+	..	+	.....
	15 yr.	F	..	+	OS slightly higher than OD; deep anterior chambers; lenses red with black rim	.....	Heart normal	+	..	+	Flexio fingers 3, 4 an

Skeletal Changes												
Long												
Feet	Arms	Legs	Kyphosis	Scoliosis	Chest	Pes Planus	Dolichocephaly	High-arched Palate	Miscellaneous	Facies	Familial Disorders	Miscellaneous
..	+	+	+	..	+	+	..	+	.....	..	No similar disease in family; father: died of pulmonary tuberculosis; mother: healthy	Syphilis; numbness, then paresis and adventitious movements of left arm; mental debilitation
+	+	+	+	+	+	..	+	+	.....	..	Mother and maternal grandmother: contractures of left 5th finger; maternal grandfather: long extremities	Cyanotic 40 min. after birth; choreiform twitches; snakelike movements of fingers
..	+	+	+	..	+	..	+	..	Talipes valgus; patella very movable	..	Maternal grandmother: epilepsy	
+	+	+	+	..	+	..	..	+	.....	..	Nephew and 2 sisters of father: harelips; father's niece: insane; mother's cousins: epileptic and mentally defective; sibs: (1) double harelip, cleft palate, (2) harelip, (3) patient, (4) long digits, (5) deaf-mute, retinitis pigmentosa, (6) double harelip, cleft palate, (7) insane, (8) died at 16 yr. of heart failure, (9) retinitis pigmentosa, deaf-mute, (10) normal	Mental defect; advanced bilateral pulmonary tuberculosis
+	+	+	.. Slight	..	..	..	..	..	.....	..	Sister: cerebroretinal degeneration; 5 first cousins; long fingers	Epilepsy at 13 yr. of age; paranoid; becoming thin; left nipple smaller than right; salt retention
..	+	..	..	..	..	..	..	..	Inturning distal phalanx 4th and 5th toes	..	.....	
+	..	..	..	..	..	..	..	..	.....	..	Parents and grandparents: well; no sibs	
..	+	+	—	+	+	+	—	+	.....	..	No blue scleras or spontaneous fractures in family; 5 healthy sisters	No spontaneous fractures; nontropical sprue; acute appendicitis
..	+	+	—	—	—	..	..	..	.....	..	Paternal grandfather: blind; father: hypertension, eyes and limbs normal; 1 brother: defective vision; 5 normal sibs	
+	..	..	+	..	+	..	..	+	.....	..	Daughter of preceding patient; mother: blind since birth; syphilis; epilepsy; systolic mitral murmur	4 wk. premature; asthma; mental retardation; negative Wassermann reaction
+	..	..	—	—	+	..	..	+	Inturning distal phalanx of outer 3 toes	..	Parents and 4 sibs: healthy	At 14 yr. of age nonrheumatic pains in muscles and joints; postmortem examination
..	..	..	..	+	..	..	..	+	.....	..	Family healthy; only child	
+	..	..	..	+	..	..	..	+	Bowing of 5th toes and fingers	..	Family healthy; only child	Soft tissue projection between 1st and 2d toes and lateral to base of 3d on left
..	+	+	..	Slight	+	..	..	+	.....	..	Parents and 4 sibs: ocular defects; no skeletal manifestations	Continuous web between 4 lateral toes, causing contracture

Author	Age	Sex	Ocular Changes: Iridodonesis	Ocular Changes: Ectopia Lentis	Miscellaneous	Aural Changes	Cardiovascular Defects	Diminished Subcutaneous Fat	Hypotonia, Atrophy, Diminished Muscle Mass	Lax Ligaments	Contracti
Filskov, A.: Ugesk. f. læger **103**: 459, 1941	21 yr.	F	..	—	Normal eyes	Thin	Apical presystolic, precordial diastolic, basal diastolic murmurs; cyanosis; congenital heart disease? hypertrophied heart; mitral stenosis	+	+	..	Early o 5th finge
Castellanos Fonseca, E.: Rev. méd-quir. de Oriente **7**:24, 1946	3½ mo.	M	..	+	Sunken eyes; OD: megalocornea, turbid humors, eccentric pupil; OS: miotic	Large; interruption of helix superiorly	Slight dilatation of all chambers on fluoroscopy; no apparent congenital heart disease; no murmur	+	+	+	Flexion elbows
Frankel, E., and White, D. N.: Clin. J. **74**: 147, 1945	27 yr.	F	+	+	Myopia; irregular pupils, dilating poorly with homatropine	.....	Creaky friction rub at end of apical systole	..	+	..	Hamm toe
Glanzmann, E.: Monatsschr. f. Kinderh. **85**: 5, 1940	11 mo.	F	..	—	Blue scleras	Large lobes; prominent anthelix	Heart normal	+	+	+	.....
	7 yr.	F	..	—	Broad sockets	.....	.....	..	..	..	.....
Gray, H.: Arch. Int. med. **75**: 215 (April) 1945	10 yr.	M	+	+	Bilateral miosis and myopia	Large	Precordial systolic murmur; apex: pair of extra sounds during systole; roentgenographic appearance normal	+	+	..	.....
Green, H., and Emerson, P. W.: Arch. Pediat. **60**: 299, 1943	2½ yr.	M	..	..	Large eyes and irises; shallow anterior chambers; glaucoma; miosis	.....	Moderately enlarged heart; no murmur	..	+	+	.....
	11 yr.	M	..	+	Myopia	.....	Extrasystoles	..	..	+	.....
	8 yr.	F	..	..	Prominent	.....	Precordial systolic thrill; loud systolic murmur; congenital heart disease	..	..	+	.....
	6½ yr.	F	+	+	.....	.....	Presystolic and systolic murmurs 2 cm. outside nipple line; later diagnosis: rheumatic heart disease, mitral stenosis	..	..	+	.....
	5 yr.	F	+	..	.....	.....	Rough precordial systolic murmur; congenital heart disease	..	..	..	Flexion knees
	9 mo.	M	+	?	Sunken; inconstant nystagmus	Large; absence of cartilage of anthelix and helix	.....	+	+	+	.....
Greiner, K., and Varga, T.: Ann. pædiat. **164**: 259, 1945	37 yr.	F	..	..	Myopia; deep; divergent latent strabismus; OS: amblyopia	.....	Heart size normal; systolic murmur	..	..	..	Elbow extens flexion 4th an fingers; hamm toe
	12 yr.	F	..	..	Deep; myopia	.....	Soft apical systolic murmur	..	..	..	Flexion elbows; claw fin
Haridas, G.: Arch. Dis. Childhood **16**: 257, 1941	7½ mo.	M	..	..	Deep; myopia; megalocornea	Large and soft	Pulmonary and tricuspid systolic murmurs; congenital heart disease	+	+	+	Flexion left thumb

Skeletal Changes												
Long												
Feet	Arms	Legs	Kyphosis	Scoliosis	Chest	Pes Planus	Dolichocephaly	High-arched Palate	Miscellaneous	Facies	Familial Disorders	Miscellaneous
+	+	+	—	—	+	..	+	+	Bilateral talipes cavus	..	Grandmother: 2 of 8 children, herself, 3 sibs and father: long hands and feet; parents and only sister without evidence of disease	Intelligence quotient, 66.3; parovarian cyst; paranoid; took poison
..	..	..	+	+	+	+	+	..	.....	+	Father, his brothers and his father: tall; Negro; no pathologic cardiac or ocular changes; mother: white	
..	+	+	..	..	+	..	+	+	.....	..	Brother: iridodonesis, ectopia, tall, muscular weakness, beginning curvature of spine; brother: curvature of spine, eyes normal, died of influenza; sister: lymphedema	Lymphedema of ankles
..	..	..	+	..	+	+	+	+	Talipes calcaneus	+	Father: tall, thin, long hands and feet; mother and her aunt: epilepsy	Palpable thyroid; much perspiration; variable temperature
+	..	..	..	..	..	..	..	..	.....	+	.....	
+	..	..	..	..	+	..	..	..	Microcephaly by measurement	..	No arachnodactyly in grandparents, parents or 5 sibs	Webbing of fingers; overlapping 2d toes; no biceps or triceps reflexes
+	..	..	..	..	+	..	..	+	Poorly developed palate; lumbar lordosis	..	Noncontributory	
+	..	..	..	..	+	..	..	..	Pronated feet	..	.....	
+	..	..	..	+	+	..	..	..	Congenital club-foot	..	Noncontributory	Died
..	..	..	..	..	..	..	..	..	Pronation and internal rotation of head of astragalus and scaphoid	..	Father: diabetes; mother and 6 sibs well	
+	..	..	..	+	+	+	..	..	.....	..	Negative family history	6 days after mastoidectomy, contracted pneumonia and died of heart failure
+	..	..	+	..	+	..	+	+	Congenital dislocation of hip and left knee; bilateral talipes calcaneovalgus; posterior luxation of left tibia on femur	..	.....	Dextroposition, not dextrocardia; pneumonia; died
+	+	..	+	+	+	..	..	..	.....	..	7 sibs healthy	
+	+	—	+	+	+	..	..	..	.....	+	Daughter of preceding patient	Positive reaction to Mantoux test; intelligence of 9 yr. old child
+	+	—	..	+	+	+	..	+	Plagiocephalism; calcaneus spur	+	Grandparents, parents and 2 brothers healthy	Cantonese; undescended right testis

TABLE 1.—*Review of Rec*

Author	Age	Sex	Ocular Changes: Iridodonesis	Ocular Changes: Ectopia Lentis	Miscellaneous	Aural Changes	Cardiovascular Defects	Diminished Subcutaneous Fat	Hypotonia, Atrophy, Diminished Muscle Mass	Lax Ligaments	Contracti
Harrison, J., and Klainer, M. J.: New England J. Med. **220**: 621, 1939	6 yr.	F	..	..	Sunken; sluggish pupillary reaction to light	Prominent; rudimentary convolutions	Thrill 3d left interspace; precordial harsh prolonged systole and part of diastole; clubbing; cyanosis; no enlargement of heart	+	+	..	Clawed hands
Jéquier, M.: Helvet. med. acta **10**: 233, 1943	12 yr.	F	..	..	Normal	.....	.....	..	..	..	.....
	15 yr.	M	..	..	.....	.....	.....	..	..	..	.....
	4 mo.	F	..	..	.....	.....	.....	..	..	..	.....
	38 yr.	F	..	..	.....	.....	.....	..	..	..	.....
	37 yr.	F	..	..	.....	Thick	.....	—	—	..	Hamm toe
	..	M	..	..	Myopia	.....	.....	..	..	..	.....
	14 yr.	F	..	..	.....	.....	.....	..	..	..	.....
	49 yr.	M	..	..	.....	.....	.....	..	..	..	.....
	12 yr.	F	..	..	Megalophthalmos; megalocornea	.....	.....	..	..	..	.....
Kahrs, T.: Acta med. Scandinav. **121**: 240, 1945	56 yr.	M	+	+	Deep anterior chamber; white cataractous substance bilaterally	.....	Aortic insufficiency; no enlargement of heart or dilatation of aorta	..	+	..	Flexio left 5th finger; hamm toe
	9 yr.	M	..	..	Normal	.....	.....	+	..	+	Hamm toe
Kilgore, G. L.: Tr. Pacific Coast Oto-Ophth. Soc. **24**: 223, 1939	33 yr.	F	—	..	Shallow coloboma of inferior margin of each lens; good vision	.....	... .	+	+	..	.....
	32 yr.	F	OD+ OS—	+ —	OD: post-traumatic retinal detachment; OS: shallow coloboma, myopia	.....	.....	+	+	..	.....
	27 yr.	F	+	+	OD: detached retina and aphakia after attempted discission, no dilation with mydriatics; OS dilatable	.....	.....	..	..	..	.....
Kovacevic, N.: Ann. pædiat. **165**: 27, 1945	10 yr.	M	..	..	Large, sunken	Large and lobular	Heart normal	+	+	..	.....

Skeletal Changes												
Long												
Feet	Arms	Legs	Kyphosis	Scoliosis	Chest	Pes Planus	Dolichocephaly	High-arched Palate	Miscellaneous	Facies	Familial Disorders	Miscellaneous
..	+	+	..	+	+	..	+	+	Hemivertebrae of lower thoracic area	..	Brother: arachnodactyly of hands and feet; mother: contractures of hands and feet, murmur; mother's sister's daughter: long fingers and toes, pigeon breast, lax ligaments; mother's brother: scoliosis, kyphosis, long fingers	At birth: blue baby and edematous
..	..	..	+	..	..	..	..	..	Anomalous ossification, from 11th dorsal to 3d lumbar vertebrae	..	These are 3 of 14 sibs born to cousins	Aplasia of rhomboid and trapezius muscles
..	..	..	..	..	..	..	..	..	.....	..		Same build as preceding patient; died at 15 yr. of age with pathologic abdominal lesions
..	..	..	..	..	..	..	..	..	.....	..		Same build as preceding patient; died
..	..	..	..	+	..	..	..	..	.....	..	Sister of next patient	Rupture of pulmonary cyst gave spontaneous pneumothorax; ptosis of gastrointestinal tract.
+	..	..	..	..	+	..	..	..	Brachycephaly	..	Sister of preceding patient	
+	..	..	..	..	..	..	..	..	.....	..	Father of 2 preceding patients	
..	..	..	Slight	Slight	..	..	..	..	Notable developmental anomalies of vertebral epiphyses; Scheuermann's disease	..	Daughter of next patient	
+	..	..	..	..	..	+	..	..	.....	..	Father of preceding patient	Strong and well built
..	..	..	..	..	..	..	..	..	Irregular epiphysial ossification in lumbar region	..	Sister: tall, big eyes	
..	..	..	..	+	+	+	..	+	Brachycephaly	..	Father's side: long, thin, with good eyesight; son: tall, thin, typical hands, ectopia, died at 19 yr. of age	
..	..	..	+	+	+	+	..	+	.....	..	Son of preceding patient; mother: father's cousin, small, stout	Webbed hands
+	+	+	—	—	..	..	..	+	.....	..	Father: 6 ft. 4 in., apparent arachnodactyly; mother: short, no ocular abnormalities; mother's family: several tall, no ocular abnormalities; brother; over 6 ft., no pathologic ocular changes; sister: short, no pathologic ocular changes	
+	+	+	..	Slight	..	..	..	..	.....	..		
+	+	+	+	+	..	..	..	+	.....	..	Sister of preceding 2 patients	
..	+	+	..	..	+	..	+	+	.....	..	Father: pulmonary tuberculosis; mother: left exudative pleurisy	Positive reaction to Pirquet test; ascaris; short esophagus with stomach above diaphragm

Author	Age	Sex	Ocular Changes: Iridodonesis	Ocular Changes: Ectopia Lentis	Miscellaneous	Aural Changes	Cardiovascular Defects	Diminished Subcutaneous Fat	Hypotonia, Atrophy, Diminished Muscle Mass	Lax Ligaments	Contractu
Krasnov, M. L.: Vestnik oftal. **18**: 198, 1941	30 yr.	F	OD+	+	OD: deep anterior chamber, eccentric pupil; OS: post-traumatic ectopia and glaucoma	.....	.....	+	+	..	.....
Lawes, F. A., and Halliday, J. C.: M. J. Australia **1**: 465, 1944	52 yr.	F	+	+	Myopia	.....	.....	..	..	..	.....
	6 yr.	M	+	+	.....	.....	.....	..	..	..	.....
Lenz, C. D.: Am. J. Ophth. **23**: 925, 1940	13 yr.	M	..	+	Cerulean cataracts	.....	.....	..	..	..	.....
Lowe, R. C.: Tri-State M. J. **13**: 2679, 1941	16 yr.	F	..	..	.....	.....	Soft apical systolic murmur; no clubbing; palpable liver; right axis deviation on electrocardiogram	..	..	+	.....
Maffei, A.: Arch. ital. di chir. **52**: 704, 1938	9 yr.	M	..	..	.....	.....	.. ..	..	+	+	.....
Mathis, G.: Rassegna ital. d'ottal. **9**: 392, 1940	7 yr.	M	+	+	Astigmatism; shallow anterior chamber; myopia	Large	.....	+	..	..	.....
	33 yr.	M	+	+	Astigmatism; oval pupils; hypermetropia; shallow anterior chamber; bilateral opaque lenses	.....	.....	..	..	..	.....
	62 yr.	F	+	+	Shallow anterior chambers; OD: myopia; OS: hypermetropia	.....	.....	..	..	..	.....
McGraw, J. L.: Arch. Ophth. **34**: 112 (Aug.) 1945	6 yr.	F	OD+	+	OD; deep anterior chamber; eccentric pupil	Prominent	.....	..	..	..	.....
Norcross, J. R.: J. Bone & Joint Surg. **20**: 757, 1938	(a) 13 yr.	M	..	..	Blue scleras	Large; diminished cartilage	Heart enlarged to left; apical thrill; diastolic murmur just inside nipple line	..	+	..	.....
	(b) 9 yr.	F	..	..	Blue scleras; slight bilateral ptosis	Large; flabby	Loud, systolic apical murmur	..	+	+	.....
	(c) 12 yr.	F	..	..	.....	.....	Systolic murmur from 2d to 4th interspaces	..	..	+	.....
	(d) 4 yr.	M	+	+	.....	.....	Systolic murmur over 2d interspace on right	..	..	..	.....
	(e) 8 yr.	M	..	+	.....	.....	.....	..	+	..	.....
	(f) .. yr.	M	..	..	.....	.....	Loud precordial diastolic murmur; blood pressure, 130/55; died of heart disease	..	..	..	.....
	(g) 2½ yr.	F	..	+	.....	.....	Pulmonary systolic murmur	..	..	..	.....
	(h) 10 yr.	F	..	..	OS: convergent strabismus and corneal leukoma	.....	Apical systolic murmur	..	+	..	.....

...erature on Arachnodactyly—Continued

Skeletal Changes												
Long												
Feet	Arms	Legs	Kyphosis	Scoliosis	Chest	Pes Planus	Dolichocephaly	High-arched Palate	Miscellaneous	Facies	Familial Disorders	Miscellaneous
+	..	..	..	..	+	Slight	..	..	.....	+	.....	Inhibited development
+	..	..	+	..	+	..	..	..	Probably healed tuberculous lesion at level of 7th thoracic vertebra	..	Daughter: long fingers; well built; when pupils dilated, iridodonesis and slight ectopia	
..	..	..	..	..	..	..	..	..	.....	+	Son of preceding patient	
..	..	..	..	..	..	..	..	..	.....	..	Father: narrow fingers, serious ocular trouble; sister: pain and diminished vision on dark days, arachnodactyly	
+	..	..	+	+	..	..	..	..	Hemivertebrae from 10th lumbar to 11th thoracic levels	..	.....	Negro; polycythemia attributed to kyphoscoliosis; cyanosis; orthopnea; cough; webbed fingers
+	+	+	..	+	..	..	..	—	Skeletal changes only on left	..		
..	+	+	..	..	+	..	..	..	.....	+	Mother: healthy; sister: normal eyes	
..	+	+	..	..	—	..	..	..	.....	..	Father of preceding patient; son of next patient	
..	..	..	..	..	..	..	..	..	.....	..	Father: ocular disturbance; 3 sibs, 9 nieces and nephews: normal eyes	
+	..	..	..	..	+	..	..	..	.....	+	Sister: ectopia, mental retardation, double 9th ribs; brother: mental deficiency and seizures, died; 2 sibs, parents and grandparents: normal	Mental retardation
+	..	..	+	+	..	..	+	+	.....	..	Family healthy, except sister, the next patient	Acrocyanosis; died of heart disease at 20 yr. of age
+	..	..	+	+	+	+	+	+	.....	..	Sister of preceding patient	Red palms
+	+	+	+	+	+	+	..	+	.....	..	Mother: normal	
+	..	..	..	..	+	..	Slight	+	.....	..	Brother of (c)	
+	..	..	+	+	+	+	..	—	Harrison's groove	..	Brother of (c) and (d)	Incomplete rotation of colon
+	..	..	..	..	+	..	+	..	.....	..	Father of (c), (d) and (e); 4th child and wife: normal	
+	..	..	..	..	..	..	..	+	Congenital dislocation of left hip	..	.....	
+	..	..	+	..	+	..	+	..	Congenital fusion of upper cervical vertebrae; hemivertebra in left cervicothoracic area; synostosis of left 1st and 2d ribs	..	.....	

Author	Age	Sex	Ocular Changes: Iridodonesis	Ocular Changes: Ectopia Lentis	Miscellaneous	Aural Changes	Cardiovascular Defects	Diminished Subcutaneous Fat	Hypotonia, Atrophy, Diminished Muscle Mass	Lax Ligaments	Contractur
Nørgaard, O.: Nord. med. (Hospitalstid.) **18**: 687, 1943	33 yr.	M	+	+	Myopia	Normal	Congenital heart disease; enlarged heart	+	+	+	–
	15½ yr.	M	..	..	Normal	.....	Apical systolic murmur (congenital or acquired?—many febrile episodes)	+	+	..	–
	24 yr.	M	..	..	Normal	.....	Normal heart	+	+	..	.....
Olcott, C. T.: Am. J. Dis. Child. **60**: 660 (Sept.) 1940	16 yr.	F	..	OS+	OS: congenital cataract; OD: removal of cataract 5 yr. previously	.....	Systolic precordial murmur; prominent chest veins; postmortem examination: heart's blood contained E. coli; perforations in posterior cusp of mitral valve	..	..	..	Hammer toes
Parker, A. S., Jr., and Hare, H. F.: Radiology **45**: 220, 1945	37 yr.	M	..	OS+	OD: normal	.....	Soft, blowing, systolic mitral murmur	+	+	+	Flexion of 2d toes
	9 yr.	F	..	+	Wide-set eyes; slight exophthalmos	.....	Systolic mitral murmur; snapping 2d sound	+	+	..	.....
	7 yr.	F	..	+	Wide-set eyes; slight congenital exophthalmos		Faint apical systolic murmur; right axis deviation; heart normal on roentgenogram	+	+	..	.....
	33 yr.	M	..	+	.....	.....	Aneurysm ascending aorta; apical and basal systolic and diastolic murmurs; gallop; congestive heart failure	+	+	..	Hammer toes
Pasachoff, H. D.; Madonick, M. J., and Drayer, C.: Am. J. Dis. Child. **67**: 201 (March) 1944	18 mo.	M	..	..	Closely set; normal	Large	Soft, systolic nontransmitted murmur to left of sternum	..	+	+	.....
	2½ yr.	F	+	+	.....	Normal	No cardiac abnormality	..	+	+	.....
	4 yr.	F	+	+	Cataract; narrow anterior chamber	.....	No cardiac abnormality	..	..	+	.....
	5½ yr.	M	+	–	.....	.....	No cardiac abnormality	..	..	..	.....
Rieken, H.: Klin. Monatsbl. f. Augenh. **105**: 482, 1940	..	F	..	+	.....	.....	.....	+	+	..	.....
	14 yr.	F	..	+	.....	.....	.....	+	+	..	.....
Schachter, M.: J. de méd. de Lyon **28**: 29, 1947	9 yr.	M	..	..	.....	.....	.....	+	..	..	.....
	15 yr.	M	..	..	Mild exophthalmos	.....	.....	..	..	..	.....
Schneider, W. F.: J. Pediat. **27**: 583, 1945	13½ yr.	F	..	+	OS: exophthalmos, exophoria, fibrous bands in vitreous; bilateral retinal detachment; glaucoma (after fall)	.....	No congenital heart disease; normal electrocardiogram	+	..	..	Flexion of elbows

Skeletal Changes													
Long													
	Feet	Arms	Legs	Kyphosis	Scoliosis	Chest	Pes Planus	Dolichocephaly	High-arched Palate	Miscellaneous	Facies	Familial Disorders	Miscellaneous
..	..	..	..	..	..	+	..	—	+	.....	..	.....	
..	..	+	+	..	..	..	Slight	+	+	.....	..	Sister: high palate; father: arachnodactyly, high palate; paternal uncle and aunt: arachnodactyly	
..	..	..	..	..	..	+	..	..	+	.....	..	No other case in family	
..	..	..	..	+	+	..	..	..	+	Bowed humeri; early closure skull and olecranon epiphyses; partial fusion distal tibiofibular epiphyses; congenital dislocation of left hip	..	Parents and sister well	Severe anemia for 3 yr.; positive reaction to tuberculin test; postmortem examination: bronchopneumonia, thyroid cyst, small adrenals, cysts of intermedia and nervosa of pituitary, hypoplastic uterus
+	+	..	..	..	+	+	+	..	—	.....	..	Two brothers: over 6 ft., thin; parents: average height	
+	..	..	..	..	..	+	+	..	+	.....	..	Daughter of preceding patient	Periodic fevers diagnosed as rheumatic
+	+	..	..	..	..	+	..	..	..	.....	..	Sister of preceding patient	
+	+	..	..	..	..	+	..	..	..	.....	..	Sister: long, slender feet and hands; parents: normal height; brothers: 5 ft. 10 in. and 6 ft.	Right lobe of thyroid 1.5 × 2 cm.; no rheumatism or syphilis in history; died in 6 mo.; no postmortem examnation
..	..	..	..	+	..	+	..	+	..	.....	+	These 4 children are siblings; paternal grandfather: tall with long fingers and toes, much difficulty with eyes, thick lenses; father: 6 ft. tall, long fingers and toes and extremities; mother: tall, slender, no ocular abnormality	13 mo. mental age; lateral ventricles moderately dilated
..	..	..	..	..	..	..	+	..	..	Genu valgum	..		Moron; slight dilatation of ventricles on lateral views of pneumoencephalogram
..	..	..	..	..	..	..	+	..	..	.....	..		Average intelligence
..	..	..	..	..	..	..	..	..	..	.....	+		
..	..	..	..	..	..	..	..	+	..	.....	..	3 normal offspring; 4 with ocular abnormalities, including son with bilateral ectopia, no other manifestations	
..	..	+	+	..	..	..	..	+	..	.....	..	Daughter of preceding patient	
..	..	..	..	..	..	..	..	..	..	Microcephaly	..	.....	Long, difficult labor: at 18 mo.: convulsions; at 4 to 9 yr.: left paresis; intelligence quotient 36; enuretic
..	..	..	..	..	..	..	..	..	..	.....	+	.....	Intelligence quotient, 47
..	..	..	..	..	..	..	+	—	..	At 4 yr. of age, fracture of neck of left femur noted on roentgenogram	..	No mental disability or congenital abnormality in family; 7 sibs: apparently of normal intelligence	Intelligence quotient, 37; fell down into cellar just previous to examination

Author	Age	Sex	Ocular Changes: Iridodonesis	Ocular Changes: Ectopia Lentis	Ocular Changes: Miscellaneous	Aural Changes	Cardiovascular Defects	Diminished Subcutaneous Fat	Hypotonia, Atrophy, Diminished Muscle Mass	Lax Ligaments	Contract
Sironi, L.: Boll. d'ocul. **18**: 671, 1939	11 yr.	M	..	+	Some depigmentation of iris	.....	.....	..	..	..	.....
Sironi: ibid. **21**: 559, 1942	8 yr.	M	+	+	Anterior chambers partly narrowed; opalescent line in lens	.....	.....	..	..	..	.....
	33 yr.	F	+	+	Myopia	.....	.....	..	..	..	.....
	35 yr.	F	+	+	Myopia	.....	Pathologic cardiac changes (type?)	+	+	..	.....
	28 yr.	F	—	+	.....	.....	.....	+	+	..	.....
	21 yr.	M	+	+	Myopia	.....	.....	..	..	..	.....
Stephenson, W. V.: Am. J. Ophth. **28**: 315, 1945	5 mo.	F	—	—	Shallow anterior chambers; corectopia; lower half of pupils v shaped; megalocornea	Normal	Heart normal	..	+	+	Clawed hand
Stern, H. J.: Brit. J. Ophth. **28**: 229 and 480, 1944	14½ yr.	M	+	+	Slightly irregularly shaped pupils; myopia; small whitish spots involving all layers near limbus; coloboma of iris	.....	Severe hypertrophy of chest veins; frequent extrasystoles	+	+	..	.....
	12 yr.	M	..	+	Diminished vision; same corneal spots and pupillary irregularity; iris with atrophic spots	.....	.....	..	..	..	.....
	(a) 14 yr.	M	+	+	Myopia	.....	Slight mitral systolic murmur	..	..	..	.....
	(b) 11 yr.	M	Slight	+	Myopia	.....	.....	..	..	..	.....
Tupinambá, J., and de Souza Dias, J.: Rev. de oftal. de São Paulo **6**: 61, 1938	11 yr.	F	+	+	.....	.....	Heart normal	..	+	..	.....
Valledor, T.; Viamonte, L., and Expósito, L.: Bol. soc. cubana de pediat. **15**: 583, 1943	12 yr.	M	..	..	Myopia	Abnormal bilaterally	.....	+[f]	+	+	Flexion knees
	5 yr.	F	+	+	Sunken eyes; hypermetropia; slight divergent strabismus	.....	Normal	+	+	+	.....
Vejdovsky, V.: Lék. listy **1**: 539, 1946	23 yr.	F	OD	+	OS: secondary cataract; OD: green opacity	.....	Dissecting ascending aortic aneurysm—ruptured; hemopericardium	..	..	..	.....

Skeletal Changes												
Long												
Feet	Arms	Legs	Kyphosis	Scoliosis	Chest	Pes Planus	Dolichocephaly	High-arched Palate	Miscellaneous	Facies	Familial Disorders	Miscellaneous
..	..	..	+	+	+	+	+	+	.....	+	Father: well; mother: died young of pathologic cardiac changes	
..	+	+	..	..	..	..	+	+	Fingers deviated on axis	..	Son of next patient	
..	+	+	..	+	..	..	..	+	Fingers deviated on axis	..	2d child died of pathologic gastrointestinal changes while young	Typhus; bronchopneumonia; many small calcified areas in lungs
+	..	..	+	+	..	..	..	..	Large capitulum of fibula	..	Sister of preceding patient	Nephritis; scattered calcifications in pulmonary areas
..	+	+	..	..	+	..	..	+	.....	..	Sister of preceding 2 patients; her daughter is normal	Left fibrous pleurisy as child
..	+	+	..	..	..	..	..	..	.....	..	Brother of preceding 3 patients; their mother had just skeletal manifestations; her father had arachnodactyly	
..	..	..	—	..	+	..	+	—	Prominent external tibial malleoli; tiny supernumerary digit, ulnar side of hand	..	5 sibs with normal corneas, but slightly increased diameters; grandparents: normal eyes	Intussusception
..	..	..	..	..	..	..	..	+	Short; gross bony trabeculation on roentgenogram; bony bridge between anterior and posterior clinoids	+	Father: asthenic, resembling sons; grandparents and 3 sibs: good eyes	Right cryptorchism; small left testis
..	..	..	..	..	..	..	..	+	Short; same trabeculation and bridge as preceding patient	+	Brother of preceding patient; father: same bridge of sella	Small, descended testes
.	..	..	..	..	..	..	..	+	Trabeculation; habitual subluxation of humerus and fingers; small sella turcica	..	Father: myopia; mother: endocrine obesity; sister: myasthenia, turned-in legs, funnel chest, myopia; sister: myopia, kyphoscoliosis, funnel chest, congenital heart disease; brother: myopia; sister: myopia; 1 healthy sister; (a) and (b) are brothers	
+	..	..	..	..	..	..	..	+	Trabeculation; subluxation of finger joints; small sella turcica	..		
..	+	+	..	..	..	..	..	..	.....	+	Parents and 11 sibs: living and well	
..	+	+	..	Slight	+	+	..	..	Exostosis from lower end of left humerus; luxation of patella; osteochondrosis of hip	+	Parents and 2 sibs: well	Muscle biopsy: no degeneration
+	+	+	..	..	..	+	..	..	.....	+	Parents well; 1 sib died of diphtheria; 2d stillborn	Normal intelligence; muscle biopsy; muscle response to faradic and galvanic currents
+	..	..	..	..	..	..	..	..	.....	..	No sibs; parents not examined	Rickets; pneumonia; 3 + Bordet-Wassermann reaction; postmortem examination: adhesive pleurisy; cardiovascular defects

TABLE 1.—*Review of Re*

Author	Age	Sex	Ocular Changes: Iridodonesis	Ocular Changes: Ectopia Lentis	Ocular Changes: Miscellaneous	Aural Changes	Cardiovascular Defects	Diminished Subcutaneous Fat	Hypotonia, Atrophy, Diminished Muscle Mass	Lax Ligaments	Contrac
Volny, K.: Lék. listy **1**: 308, 1946	12 yr.	F	OD	+	Sunken OD; deep anterior chambers; right pupil smaller than left	.....	Mitral and pulmonary systolic murmurs; mitral insufficiency; left ventricular hypertrophy; slight cyanosis; extrasystoles after exertion	+	+	..	.....
von Bahr, G.: Nord. med. **10**: 2020, 1941	11 yr.	F	..	+	.....	.....	Soft apical systolic murmur	..	..	..	.....
Wahl, M., and Schachter, M.: Arch. de méd. d. enf. **43**: 37, 1940	15 yr.	F	..	..	Normal except for frequent blinking	.....	.....	+	+	+	Flexio elbow
Wyckoff, H. J.: Northwest Med. **38**: 134, 1939	17 yr.	M	..	+	.....	.....	Congenital heart disease with loud blowing sounds at apex and base	+	..	+	Clawi all toe
	14 yr.	F	..	..	Myopia	.....	Soft apical murmur; mild cyanosis	..	..	..	.....
	15 yr.	F	..	..	Myopia	.....	Blow over heart midway between apex and aortic valve; cyanotic	..	..	..	.....
Total.....					87	21	26	48	51	37	28

skeletal abnormality. Forty per cent had high-arched palates. Slightly over one fifth of the patients had congenital cardiovascular anomalies and a little less than one-fifth had abnormalities of the external ear. There was no striking sex distribution either so far as the total number of cases of arachnodactyly was concerned or in reference to any one anomaly, except (what is of doubtful statistical significance) that more males (13) than females (8) had aural defects; the latter finding was noted by Rados in his series, too. However, the greater incidence of ocular signs in males as compared with females in Rados' group of patients was not observed in the present study, in which the figures were the same for both sexes. In this series there was a greater percentage (56 per cent) of patients having a positive hereditary history than in Rados'. When two anomalies were coexistent in a patient with arachnodactyly, they were most frequently ectopia lentis and high-arched palate. The commonest set of three associated anomalies was ectopia lentis, cardiovascular defect and high-arched palate. No description of a patient manifesting all the possible abnormalities of the syndrome was found.

erature on Arachnodactyly—Continued

Skeletal Changes												
Long												
Feet	Arms	Legs	Kyphosis	Scoliosis	Chest	Pes Planus	Dolichocephaly	High-arched Palate	Miscellaneous	Facies	Familial Disorders	Miscellaneous
+	..	..	..	..	..	+	..	..	.....	..	Negative family history	Slight thyroid enlargement
.	..	..	..	+	+	..	..	+	.....	..	No tall, thin people in the family	
+	..	..	..	..	..	..	+	..	Right upper canine tooth is supernumerary	..	Parent and 2 sibs: healthy	Imbecile; mild choreoathetosis; retarded sexual development
..	+	+	+	+	+	..	+	+	.....	..	.....	Undescended testes
..	..	..	..	+	..	..	..	+	.....	..	.....	
..	..	..	+	+	..	..	..	+	.....	..	.....	
								47				
					83					23	66	

TABLE 2.—*Various Combinations of Abnormalities in Patients with Arachnodactyly*

Ectopia Lentis	Aural	Cardio-vascular	Dolicho-cephaly	High Palatal	Male History		Female History		Total
					Positive	Negative	Positive	Negative	
+	..	..	..	..	22	10	17	15	64
..	+	..	..	..	5	8	6	2	21
..	..	+	..	..	6	5	5	10	26
..	..	..	+	..	9	6	8	6	29
..	..	..	..	+	13	12	14	8	47
+	+	..	..	..	2	3	0	0	5
+	..	+	..	..	4	3	2	5	14
+	..	..	+	..	5	3	3	2	13
+	..	..	..	+	9	5	7	7	28
..	+	+	..	..	1	2	2	2	7
..	+	..	+	..	4	3	3	1	11
..	+	..	..	+	2	5	4	0	11
..	..	+	+	..	3	1	2	3	9
..	..	+	..	+	4	5	4	3	16
..	..	..	+	+	4	4	5	2	15
+	+	+	..	..	0	1	0	0	1
+	+	..	+	..	1	1	0	0	2
+	+	..	..	+	0	1	0	0	1
+	..	+	+	..	1	1	0	1	3
+	..	+	..	+	3	3	2	2	10
+	..	..	+	+	3	1	1	2	7
..	+	+	+	..	1	0	2	1	4
..	+	+	..	+	1	1	2	0	4
..	+	..	+	+	1	2	3	0	6
..	..	+	+	+	2	1	2	1	6
+	+	+	+	..	0	0	0	0	0
+	+	+	..	+	0	1	0	0	1
+	+	..	+	+	0	0	0	0	0
+	..	+	+	+	1	1	0	1	3
.	+	+	+	+	1	0	2	0	3
+	+	+	+	+	0	0	0	0	0
					32	24	34	27	117
					56		61		

SUMMARY

A patient with arachnodactyly with cleft palate, a combination heretofore described in only 2 persons, is reported on, and a summary of the recent literature on arachnodactyly is made. The patient described had long thin fingers and feet, pointed ears and an old, sad expression. No ocular, chest or cardiac abnormality could be detected by physical examination.

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Dr. J. Buren Sidbury gave permission to report on this patient; Dr. Daniel M. Thomas (now of Duke Hospital, Duke University, Durham, N. C.) made the diagnosis of arachnodactyly, and they and Dr. Joseph C. Knox provided comment on the case.

TREATMENT OF SCARLET FEVER WITH HUMAN IMMUNE GLOBULIN

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HUMAN immune globulin, U.S.P. (gamma globulin) is present in fraction II of pooled human plasma.[1] Its concentration of antibodies is stated to be approximately twenty-five times the concentration of antibodies in pooled normal adult plasma.[2] Human immune globulin has been shown capable of preventing or attenuating measles.[3] While ordinary human immune globulin is ineffective in protecting exposed susceptible persons against mumps,[2b] human immune globulin derived from mumps convalescent serum has been reported to reduce the incidence of orchitis in United States Army personnel with mumps to 7.8 per cent.[4] In patients treated without human immune globulin or with ordinary human immune globulin, the incidence of orchitis approximated 27 to 33 per cent.

Human immune globulin has also been shown effective in passive immunization against infectious hepatitis,[5] although there is thus far no

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(Footnote continued on next page)

conclusive evidence of its value in treatment of that disease. Human immune globulin appears to prolong the incubation period of, and possibly protect against, homologous serum hepatitis.[6] Although human immune globulin possesses neutralizing antibodies against poliomyelitis virus, treatment of animals inoculated with the virus intracerebrally has proved ineffective even when given early in the incubation period.[7]

The quantity of scarlet fever streptococcus antitoxin in the globulin concentrates of fraction II of pooled human plasma was reported by Enders to be more than three times the quantity in convalescent serum.[8] Titration of a sample lot of human immune globulin [9] used in this study showed it to contain 40 neutralizing units per cubic centimeter.[10] The scarlet fever streptococcus antitoxin U.S.P. used in this study contained 3,500 neutralizing units per cubic centimeter.[11] It is apparent that the titrational values of human immune globulin are not comparable with those of commercially prepared horse serum antitoxin.

Scarlet fever streptococcus antitoxin has been shown highly effective in reducing the toxicity and febrile course of scarlet fever, in reducing the extent and duration of the cutaneous lesions and in reducing the incidence, severity and duration of complications.[12] Severe and frequent reactions are not encountered with the new, refined serum.[13] Similar and

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often superior therapeutic results, despite the much lower antitoxin content, were shown with the use of pooled convalescent serum.[14] Top and Young [15] observed that convalescent serum and streptococcus antitoxin were equally effective. They suggested that the efficacy of convalescent serum, surprising in view of its low antitoxin content, might be due to the presence of an antibacterial substance and augmentation of its effect by the small amount of antitoxin.

It was the purpose of the present study to compare the effect of human immune globulin and scarlet fever streptococcus antitoxin prepared in horses on the course of scarlet fever, in order to determine which exercised a more favorable influence on the febrile course, the cutaneous lesions and the incidence of complications.

PLAN OF STUDY

The study material consisted of all patients with scarlet fever admitted to the service of Dr. John A. Toomey, Department of Contagious Diseases, City Hospital, Cleveland, from Jan. 17, 1946 to Feb. 5, 1947. The diagnosis of scarlet fever was made on the basis of clinical criteria, namely, the presence of a characteristic papular erythematous rash, pharyngitis, tonsillitis (except in cases of surgical scarlet fever) and fever. Routine nose and throat cultures were not made throughout the study.

Eight patients with surgical scarlet fever were included in the study (1 patient in the group given human immune globulin, 4 in the group given antitoxin and 3 patients in the controls).

The great majority of the patients had had the rash for two days or less on admission, and all patients who had had the rash for more than three days were excluded from this study. In two exceptions, there was reason to doubt the accuracy of the reported duration of the rash. Also excluded were all patients for whom the clinical diagnosis of scarlet fever was not reasonably certain or in whom another infectious disease was present in addition to scarlet fever.

Originally, it was proposed to treat successive patients admitted with (1) human immune globulin, (2) scarlet fever streptococcus antitoxin and (3) no specific procedure. But because the therapeutic value of human immune globulin was unknown, penicillin was given in addition to globulin or antitoxin to the 6 severely ill patients. Furthermore, the controls were not always used in unselected successive rotation; but the control group was composed of patients concomitantly admitted with those selected for the two specifically treated groups, and controls were obtained in the final, as well as in the early, weeks of the study.

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Severity of the disease on admission to the hospital was graded on the degree of fever, the pulse rate and the general appearance of the patient. As seen from table 1, the control group contained a somewhat higher percentage of patients with mild attacks (93.1 per cent as compared with 89.6 per cent in the globulin group and 82.4 per cent in the scarlet fever antitoxin group) because several patients with forms too mild to be useful in determining the efficacy of human immune globulin or scarlet fever antitoxin were used as controls.

TABLE 1.—*Severity of Disease on Admission*

	Human Immune Globulin, 106 Patients		Scarlet Fever Streptococcus Antitoxin, 108 Patients		Controls, 72 Patients	
	No.	%	No.	%	No.	%
Mild	95	89.6	89	82.4	67	93.1
Moderate	10	9.4	14	13.0	5	7
Severe	1	0.9	5	4.6	..	....

TABLE 2.—*Duration of Rash Prior to Treatment or Observation*

Duration, Days	Human Immune Globulin, 106 Patients		Scarlet Fever Streptococcus Antitoxin, 108 Patients		Controls, 72 Patients	
	No.	%	No.	%	No.	%
1	85	80.2	85	78.7	52	72.2
2	13	12.3	19	17.6	7	9.7
3	5	4.7	3	2.8	13	18.1
4	* 1	0.9	..	....	..	....
5	..	....	..	....	..	....
6	..	....	..	....	..	....
7	* 1	0.9	..	....	..	....
8	..	....	..	....	..	....
Unknown	..	....	1	0.9	..	....

* In each patient there was reason to doubt accuracy of reported duration of rash.

TABLE 3.—*Duration of Symptoms Prior to Treatment or Observation*

Duration, Days	Human Immune Globulin, 106 Patients		Scarlet Fever Streptococcus Antitoxin, 108 Patients		Control Group, 72 Patients	
	No.	%	No.	%	No.	%
1	38	35.8	42	38.9	23	31.9
2	25	23.6	33	30.6	16	22.2
3	24	22.7	16	14.7	22	30.6
4	12	11.3	11	10.2	8	11.1
5	1	0.9	3	2.8	3	4.2
6	1	0.9	2	1.9	..	....
7	3	2.8	..	....	..	....
8	1	0.9	..	....	..	....
Unknown	1	0.9	1	0.9	..	....

The control group had a higher percentage of patients whose rash had been present three days before they came under observation (18.1 per cent compared with 4.7 per cent in the globulin-treated group and 2.8 per cent in the antitoxin-treated group). This is shown in table 2. However, neither of these circumstances lessens the value of the control group in the study of the complications of the disease, as will be seen from the data presented later. Table 3 shows the duration of symptoms among the three groups prior to treatment or observation.

A number of patients in each of the groups was given penicillin or a sulfonamide drug (sulfadiazine) on admission because of the presence of a complication, such as otitis media or unusually severe pharyngitis or tonsillitis, or because of the severity of the illness. Many patients received such additional therapy when a

TABLE 4.—*Patients Receiving Additional Therapy*

Additional Therapy	Days Given After Admission	Human Immune Globulin, 106 Patients No.	%	Scarlet Fever Streptococcus Antitoxin, 108 Patients No.	%	Control Group, 72 Patients No.	%
Penicillin	1 to 5	7	6.6	18	16.6	15	20.8
Penicillin	6 to 21	6	5.6	12	11.1	2	2.7
Sulfonamide drugs	1 to 5	19	17.9	20	18.5	14	19.5
Sulfonamide drugs	6 to 21	7	6.6	8	7.4	3	4.2

TABLE 5.—*Age Distribution*

Age, Yr.	Human Immune Globulin, 106 Patients No.	%	Scarlet Fever Streptococcus Antitoxin, 108 Patients No.	%	Controls, 72 Patients No.	%
Less than 5	32	30.2	29	26.9	18	25
5 to 10	46	43.4	41	38.1	31	43.1
11 to 20	20	18.9	28	25.9	14	19.5
21 to 30	2	1.9	5	4.6	5	7
31 to 40	3	2.8	3	2.8	3	4.2
41 to 50	2	1.9	1	0.9	1	1.4
More than 50	1	0.9	1	0.9	..	....

TABLE 6.—*Severity of the Rash*

Degree of Rash	Human Immune Globulin, 106 Patients No.	%	Scarlet Fever Streptococcus Antitoxin, 108 Patients No.	%	Controls, 72 Patients No.	%
+	21	19.8	11	10.2	22	30.6
++	82	77.4	88	81.5	46	64
+++	3	2.8	7	6.5	4	5.6
++++	..	....	2	1.8	..	....

TABLE 7.—*Distribution According to Race*

	Human Immune Globulin, 106 Patients No.	%	Scarlet Fever Streptococcus Antitoxin, 108 Patients No.	%	Controls, 72 Patients No.	%
White	88	82.9	94	87	50	69.5
Negro	18	17	14	13	22	30.5

septic complication appeared. All patients who had received any sulfonamide compound or penicillin therapy prior to admission were considered as having received additional therapy during the first four days (table 4).

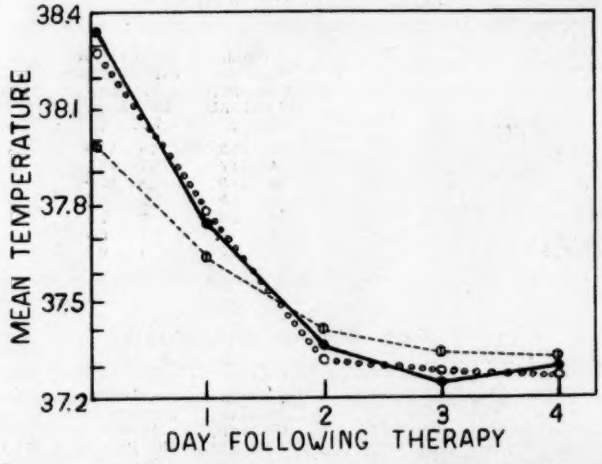
Table 5 shows the age distribution of the three groups. It illustrates that they were reasonably well apportioned as to age.

Table 6 shows the severity of the rash in the three groups. A rash was called "1 plus" when only papillation existed. "Two plus" and "3 plus" described different degrees of intensity of an erythematous, papular rash, while a rash which showed petechiae or larger hemorrhages was called "4 plus."

Table 7 shows the percentage of white and Negro patients in each group.

The observation of the patients was carried out by one person except for a three week interval when another observer was substituted. With rare exceptions, the patients were observed for at least three weeks.

Dosage.—Human immune globulin was administered in amounts of 1 cc. per pound (0.5 Kg.) of body weight, up to 60 cc. No dose of human immune globulin greater than 60 cc. was given. The dose of scarlet fever streptococcus antitoxin was 9,000 units for the person with the mild form. Some of those with the moderately severe disease received 9,000 units and others 18,000 units. The entire dose of human immune globulin or scarlet fever antitoxin was given at one time.



Graph showing curves for mean temperatures during first four days after treatment. The line composed of circles indicates the mean for 74 patients treated with scarlet fever antitoxin; the solid line that for 83 patients treated with gamma globulin, and the broken line that for 50 controls.

RESULTS

From Jan. 17, 1946 to Feb. 5, 1947, 106 patients with scarlet fever were treated with human immune globulin; 108 patients were treated with scarlet fever antitoxin, and there were 72 controls. After exclusion of all patients who received additional therapy during the first four days, there were left 83 who were treated with human immune globulin, 74 who were treated with scarlet fever antitoxin and 50 controls.

Fever.—Rectal temperatures were recorded every six hours, and the mean of the highest and lowest temperature for each twenty-four hour period of the first four days following specific treatment was obtained. Curves for temperature in the figure represent averages of mean temperatures for each of the first four days in each group. All patients

who received penicillin or sulfadiazine prior to or during this period were excluded.

It may be seen that there is little difference in the course of the composite temperature curves of the patients treated with human immune globulin and those treated with scarlet fever antitoxin. The control group, containing patients with the milder disease, showed a lower mean temperature for the first day; nevertheless, the mean temperatures of both specifically treated groups were slightly lower than those of the controls by the latter part of the second day.

Fading of the Rash.—Table 8 shows the percentage of patients in each group whose rash had faded by successive twenty-four hour periods.

TABLE 8.—*Fading of the Rash*

	Human Immune Globulin, 83 Patients		Scarlet Fever Streptococcus Antitoxin, 74 Patients		Controls, 50 Patients	
	No.	%	No.	%	No.	%
No. of patients in whom fading was observed	56	67.5	53	71.5	26	52
Faded, 24 hr	37	66	40	75.5	17	65.4
25 to 48	17	30	13	24.5	6	23
49 to 72	..	....	..	....	1	3.8
73 to 96	2	3.6	..	....	..	....
More than 96	..	....	..	....	2	7.7

TABLE 9.—*Complication Rate*

	Human Immune Globulin, 83 Patients		Scarlet Fever Streptococcus Antitoxin, 74 Patients		Controls, 50 Patients	
	No.	%	No.	%	No.	%
Patients with complications, excluding those receiving additional therapy prior to appearance of complication	21	25.6	32	43.3	16	32

The observation of fading time was made and recorded in 67.5 per cent of the group treated with human immune globulin, 71.5 per cent of the group treated with scarlet fever antitoxin and 52 per cent of the control group. In 75.5 per cent of those in the antitoxin-treated group the rash had faded in twenty-four hours as compared with 66 per cent in the globulin-treated group. This tendency to slightly more rapid fading in the antitoxin-treated group is not large enough to be significant. The rash in the controls showed a tendency to fade more slowly; while in 65.4 per cent of the controls the fading occurred in the first twenty-four hours, a higher rate of early fading would be expected in this group because of the greater proportion whose rash had already been present three days (table 2).

Complications.—Table 9 shows the complications in the three groups after exclusion of all patients who received penicillin or a sulfonamide

compound prior to or during the first four days in the hospital. Only those complications were considered which developed forty-eight hours or more after admission. It is shown that complications in the group given scarlet fever antitoxin occurred in 43.3 per cent of patients as compared with 25.6 per cent in the group given human immune globulin and 32 per cent in the control group.

Table 10 shows that a large number of the complications in the antitoxin-treated group were febrile recurrences. These were arbitrarily

TABLE 10.—*Incidence of Individual Complications*

Type of Complication	Group Given Human Immune Globulin No.	%	Group Given Scarlet Fever Streptococcus Antitoxin No.	%	Controls No.	%
Febrile recurrence	8	7.5	20	18.5	8	11.1
Cervical adenitis	1	0.9	4	3.7	2	2.8
Tonsillitis and/or pharyngitis	5	4.7	11	10.2	5	7
Otitis media	6	5.7	6	5.6	5	7
Paronychia	2	1.9	..	....	1	1.4
Sinusitis	1	0.9	1	0.9	2	2.8
Rheumatic fever, new cases	1	0.9	..	....	..	....
Rheumatic fever, cases with history of previous attacks	1	0.9	2	1.8	..	....
Abscess of the leg	..	....	1	0.9	..	....
Peritonsillar abscess	1	0.9	..	....	..	....
Bronchopneumonia	..	....	2	1.8	..	....
Recurrent scarlet fever	..	....	..	....	1	1.4
Pyelonephritis	..	....	1	0.9	..	....

TABLE 11.—*Corrected Complication Rate*

	Human Immune Globulin, 83 Patients No.	%	Scarlet Fever Streptococcus Antitoxin, 74 Patients No.	%	Controls, 50 Patients No.	%
Patients with complications, excluding those receiving additional therapy prior to appearance of complication and disregarding febrile recurrences	13	15.7	19	25.6	12	24

defined as a recurrence of fever, at 38 C. (100.4 F.) or higher, for two days or more in succession, on or after the eighth day in the hospital, and in the absence of other demonstrable complications. Since it was felt that many of the febrile recurrences in the group given scarlet fever antitoxin represented mild, unrecognized serum sickness, a corrected complication rate was made in table 11, in which febrile recurrences were disregarded in all three groups. Here it is seen that the percentage of patients with complications in the control and the antitoxin-treated groups is the same (24 and 25.6 per cent, respectively), while the percentage of complications among the globulin-treated group is somewhat lower (15.7 per cent).

A number of patients, as was stated, received sulfadiazine or penicillin, or both, prior to or during the first four days of observation. After omission from this group of patients of all those in whom a complicating factor was already present on admission, the group was studied for the development of subsequent complications (table 12). It is seen that of 27 patients receiving early additional therapy of this nature, only

TABLE 12.—*Complications in Patients with Additional Therapy (Patients Who Received Sulfonamide or Penicillin from Admission and Who Had No Complication on Admission)* *

	Group Given Human Immune Globulin	Group Given Scarlet Fever Strepto-coccus Antitoxin	Controls	Total No.	Total %
Received penicillin from admission:					
No complication	1	7	6	14	
Complication	0	1 Febrile recurrence	1 Febrile recurrence	2	14.3
Received sulfonamide drugs from admission:					
No complication	3	1	4	8	
Complication	0	0	1 Febrile recurrence	1	12.5
Received sulfonamide drugs and penicillin from admission:					
No complication	3	1	1	5	
Complication	1 Febrile recurrence	0	0	1	20.0
Total receiving additional therapy from admission:					
No complication	7	9	11	27	
Complication	1 Febrile recurrence	1 Febrile recurrence	2 Febrile recurrence	4	14.8

*Any patient who had received a sulfonamide drug or penicillin prior to admission was also included in this category.

TABLE 13.—*Serum Reactions*

	Group Given Human Immune Globulin		Scarlet Fever Streptococcus Antitoxin	
	No.	%	No.	%
Urticaria	2	1.9	4	3.7
Arthralgia and fever	..	...	1	0.9
Maculopapular rash	..	...	1	0.9
Total	2	1.9	6	5.5

4 had subsequent complications and these were all of the febrile recurrence type.

Table 10 shows the variety and number of complications that occurred. One patient with recurrent scarlet fever, with reappearance of the rash, pharyngitis and fever, was observed in the control group. There were 4 patients with rheumatic fever,[16] 2 in the globulin-treated

16. Criteria used in making a diagnosis of rheumatic fever were those employed by Dr. T. Duckett Jones (The Diagnosis of Rheumatic Fever, *J. A. M. A.* **126**: 481-486 [Oct. 21] 1944).

group and 2 in the antitoxin-treated group. One of the patients in the globulin-treated group and both of those in the antitoxin-treated group had histories of previous attacks of rheumatic fever.

Reactions.—Table 13 shows the reactions which occurred from treatment with human immune globulin or scarlet fever streptococcus antitoxin. These total 1.9 per cent in the group given human immune globulin and 5.5 per cent in the group given scarlet fever antitoxin.

COMMENT

Despite the greater potency of antitoxin in neutralizing power against the erythrogenic scarlet fever streptococcus toxin, the effect of human immune globulin on the toxemia (as measured by fall in temperature) seems to be approximately the same. Hirsh and his associates compared the effect of penicillin and antitoxin on the temperature in scarlet fever and observed that the "average duration of fever" in the patients treated with scarlet fever antitoxin was twenty-nine hours compared with fifty hours for those treated with penicillin and ninety-nine hours for the controls.[17] Hoyne and Brown, however, observed about the same duration of fever in patients treated with convalescent serum (3.49 days) and in those treated with penicillin (3.46 days).[18]

Again, despite the discrepancy in antierythema potency of the two agents compared in this present series, little difference was seen in their effect on the rash of scarlet fever. The controls, as would be expected, showed somewhat slower fading. Hirsh and his associates were of the opinion that in patients treated with penicillin the rash disappeared more quickly than in controls,[17] while Hoyne and Brown reported the duration of the rash shorter among those in the penicillin-treated group than among those treated with convalescent serum or sulfonamide drugs or the controls.[18] The latter authors, however, stated that their penicillin-treated patients had been ill longer on admission than patients in the other groups.

The most interesting observation in the study was the lower incidence of complications in the globulin-treated group (15.7 per cent) compared with 24 per cent in the controls and 25.6 per cent in the antitoxin-treated group.

Hirsh and his co-workers had 26 per cent complications in the milder control group, 44 per cent complications in the antitoxin-treated group and 10 per cent in the penicillin-treated group.[17] The complications in the penicillin-treated group were all mild forms of recurrent

17. Hirsch, H. L.; Rotman-Kravka, G.; Dowling, H. F., and Sweet, L. K.: Penicillin Therapy of Scarlet Fever, J. A. M. A. **133**:657-661 (March 8) 1947.

18. Hoyne, A. L., and Brown, R. H.: Penicillin for Scarlet Fever, J. A. M. A. **133**:661-663 (March 8) 1947.

pharyngitis. The total of patients in each group, however, was small (25 patients treated with antitoxin and 29 treated with penicillin).

Hoyne and Brown had 18.58 per cent complications in their controls, 37.67 per cent complications in the group treated with convalescent serum, 31.25 per cent complications in the group treated with sulfonamide drugs and 15.51 per cent complications in the group treated with penicillin.[18] The low complication rate in the controls may have resulted from the greater proportion of patients with mild forms in that group.

Breese and his associates (Epidemiology Unit No. 82) observed that in patients treated with penicillin a dosage of 240,000 units spread over three days gave a complication rate of 31 per cent, while 480,000 units over eight days gave a rate of only 6 per cent.[19]

Ashley, likewise, reported that patients treated with penicillin and convalescent serum had less complications than patients treated with either convalescent serum alone or antitoxin alone.[20]

The present series showed no significant differences in the type of complications occurring in the globulin-treated and antitoxin-treated groups. It is interesting to note (table 12) that of the 27 patients given globulin or antitoxin and used as controls who also received penicillin or sulfadiazine or both on admission, only 4 patients showed complications and those were all of the febrile recurrence type.

Dick and Dick were of the opinion that only toxigenic streptococci were invasive (i. e., responsible for complications) and concluded that for invasion (complication) to occur the tissues must first be injured by toxin.[12d] They stated that scarlet fever antitoxin reduced the number and severity of complications. The present series showed the incidence of complications to be the same in patients treated with antitoxin and in controls.

The apparently equal efficacy of human immune globulin and scarlet fever streptococcus antitoxin in influencing temperature and the somewhat superior efficacy of the former in preventing complication suggest that an additional factor, perhaps antibacterial, may be present in human immune globulin, since its antitoxin content is scarcely comparable to that of commercially prepared antitoxin. In patients treated with human immune globulin who received the maximum amount of 60 cc., the total amount of antitoxin given, according to the assay referred to, would be 60×40 or 2,400 units, as compared with the minimum dose of 9,000 units in those treated with the commercial antitoxin.

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19. Observations on the Treatment of Scarlet Fever with Penicillin, Epidemiology Unit No. 82, United States Naval Hospital, Treasure Island, Am. J. M. Sc. **211**:417-420 (April) 1946.

20. Ashley, P.: Treatment of Scarlet Fever, J. A. M. A. **130**:771-774 (March 23) 1946.

The 6 most severely ill patients received penicillin in addition to globulin or antitoxin and were, therefore, excluded. Hence, it is not possible from this study to judge the value of globulin for patients with pronounced toxemia.

SUMMARY

1. From Jan. 17, 1946 to Feb. 5, 1947, 106 patients with scarlet fever were treated with human immune globulin U. S. P., 108 were treated with scarlet fever streptococcus antitoxin U. S. P., and there were 72 controls. After exclusion of patients who had received penicillin or sulfadiazine during the first four days, there remained 83 treated with human immune globulin, 74 patients treated with scarlet fever antitoxin and 50 controls.

2. Human immune globulin and scarlet fever streptococcus antitoxin affected the temperature and accelerated the fading of the rash in like manner and degree.

3. There were fewer complications (15.7 per cent) in patients treated with human immune globulin than in those treated with scarlet fever antitoxin (25.6 per cent). In the untreated controls who had somewhat milder attacks, the complications were about the same as in the antitoxin-treated groups (24 per cent).

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Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

ABNORMAL WATER METABOLISM IN MALNUTRITION. M. LAMY, M. LAMOTTE and S. LAMOTTE-BARRILLON, Presse méd. **54**:621 (Sept. 28) 1946.

In 40 persons with malnutrition returned from German concentration camps, edema was observed at some time or other in 34. The location and extent of the edema were variable. In the dehydrated persons, the authors observed that the administration of fluid parenterally produced pulmonary edema and cardiac failure. Best results were obtained by complete rest in bed, limitation of fluids taken by mouth and administration of a high protein, high vitamin diet.

DAFFINEE, Melrose, Mass.

MEAT JUICE IN THE FEEDING OF INFANTS. F. ESCARDO and M. WAISSMANN, Arch. argent. de pediat. **26**:336 (Nov.) 1946.

A review of the literature and an analysis of meat juice permit the following conclusions: In the form in which it is usually prepared and in the doses used, meat juice has no nutritive value. Therefore, the current idea that meat juice serves as an initiation to or substitute for feeding with meat should be rejected. The salt content of meat juice has no nutritive value in the diet of the second six months. Its use is justified only to accustom babies to strong salty flavors. Experience shows that the administration of meat juice to some neuropathic or excitable children results in irritability.

ROJAS, Boston.

Vitamins; Avitaminoses

THE RENAL THRESHOLD FOR ASCORBIC ACID: A MODIFIED METHOD FOR ITS ESTIMATION WITH RESULTS FOR TWELVE ADULT SUBJECTS. ANN MOORE KLOSTERMAN, J. ESTELLE HAINES, HAZEL M. HAUCK and ALICE B. KLINE, J. Nutrition **33**:505 (May) 1947.

Klosterman and her associates presented a modified method for estimation of the renal threshold for ascorbic acid, based on the comparison of means and standard deviations for urinary excretions at various plasma ascorbic acid levels. The renal threshold for the 12 normal adults was between 1 and 1.3 mg. per hundred cubic centimeters. The renal threshold for ascorbic acid was observed to be relatively stable from year to year.

FREDEEN, Kansas City, Mo.

A STUDY OF ASCORBIC ACID METABOLISM OF ADOLESCENT CHILDREN. CLARA A. STORVICK, MARGARET L. FINCKE, JEANNE PERKINS QUINN and BESSIE L. DAVEY, J. Nutrition **33**:529 (May) 1947.

Storvick and her associates present data showing that mean fasting values for ascorbic acid of 0.9 to 1.2 mg. per hundred cubic centimeters of plasma were maintained by the 4 adolescent girls on the allowance recommended by the National Research Council and equivalent to 1.3 to 1.7 mg. per kilogram of body weight. The National Research Council's allowance, which was equivalent to 1.9 to 2.1 mg. per kilogram of body weight for the 4 boys, maintained mean fasting values from 0.8 to 1 mg. per hundred cubic centimeters of plasma during the last five days for the one week period on this intake. For these young adolescents, the allowances of ascorbic acid recommended by the National Research Council resulted in fasting values for ascorbic acid in the plasma below those individually attained

when saturation doses were given, although for one week these allowances were adequate to maintain plasma values which are associated with "good" stores of ascorbic acid. This first study on the ascorbic acid requirements of young adolescent boys and girls suggests that they may require somewhat more ascorbic acid per kilogram of body weight to maintain saturation than do younger children or adults.

FREDEEN, Kansas City, Mo.

METABOLISM OF WOMEN DURING THE REPRODUCTIVE CYCLE: VITAMIN C IN DIETS, BREAST MILK, BLOOD AND URINE OF NURSNG MOTHERS. BERTHA MUNKS, MILDRED KAUCHER, ELSIE Z. MOYER, MARY E. HARRIS and ICIE MACY, J. Nutrition **33**:601 (June) 1947.

Vitamin C was determined by analysis in the food as eaten each day by healthy nursing mothers and in twenty-four hour collections of their milk and urine during the first ten days post partum and during five day periods at intervals later in lactation. In addition, the amount of vitamin C was determined in blood from the umbilical cord and in fasting samples of capillary blood from mothers and infants.

Munks and her co-workers observed that the amounts of vitamin C secreted in milk paralleled the increases in milk volume, while vitamin C excretion in the urine was high after delivery, and for 3 or 4 mothers decreased 50 per cent or more by the tenth day. No relationships between volume of milk or its vitamin C content and excretion of the vitamin in the urine were indicated. During the periods of secretion of mature milk, the amounts of vitamin C in the milk paralleled milk volume. Extreme anatomic and physiologic variability among persons and in the same person at different times is emphasized by the results. On the basis of the data presented, it seems that the recommended dietary allowances supply adequate amounts of vitamin C to meet normal requirements during lactation, provided the prenatal nutritional status of the mother has been satisfactory.

FREDEEN, Kansas City, Mo.

METABOLISM OF WOMEN DURING THE REPRODUCTIVE CYCLE: THE EFFECT OF MULTI-VITAMIN SUPPLEMENTS ON THE VITAMIN C UTILIZATION OF NURSING MOTHERS. J. P. PRATT, BERTHA MUNKS and ICIE G. MACY, J. Nutrition **33**:621 (June) 1947.

Although the average levels of vitamin C in the breast milk and in fasting blood samples were higher following supplementation of the diet with the administration of 750 mg. of ascorbic acid per day for six to fourteen days, the major portion of the ascorbic acid given was represented by increases in urinary excretion. Pratt and his co-workers from their data suggest that the amount of vitamin C recommended by the Food and Nutrition Board of the National Research Council for lactating women is sufficient when supplied by natural foods in a diet adequate with respect to other dietary essentials and when during pregnancy the nutritional status of the mother has been satisfactory.

FREDEEN, Kansas City, Mo.

THE AVAILABILITY OF VITAMINS FROM YEASTS: THE AVAILABILITY TO HUMAN SUBJECTS OF RIBOFLAVIN FROM FRESH AND DRIED BAKERS' YEASTS VARYING IN VIABILITY. ECHO L. PRICE, MONA M. MARQUETTE and HELEN T. PARSONS, J. Nutrition **34**:311 (Sept.) 1947.

Price and her associates studied the degree of absorption of riboflavin of various yeasts from the digestive tract as judged by urinary excretions and, in some experiments, fecal outputs, with the use of human bioassay methods. Their results support the hypothesis that the tenacity of the living yeast cell was responsible for withholding the riboflavin from absorption.

FREDEEN, Kansas City, Mo.

THE AVAILABILITY OF VITAMINS FROM YEASTS: THE INFLUENCE OF THE INGESTION OF FRESH AND DRIED BAKERS' YEASTS VARYING IN VIABILITY AND IN THIAMINE CONTENT ON THE AVAILABILITY OF THIAMINE TO HUMAN SUBJECTS. HELEN KESS KINGSLEY and HELEN T. PARSONS, J. Nutrition **34**:321 (Sept.) 1947.

Kingsley and Parsons concluded that thiamine in an unfortified, fresh bakers' yeast ingested by human subjects was unavailable for absorption. Yeasts high in thiamine content, from either propagation or fortification, yielded only a small proportion of their thiamine for absorption; in the case of the highly fortified yeast a much larger proportion of thiamine was released in vitro in comparison. The ingestion of a fresh unfortified bakers' yeast as a supplement to a weighed basal diet lowered the urinary output of thiamine and, therefore, apparently interfered with the absorption of thiamine from food, this effect being greater on the larger dose of 150 Gm. of yeast per day. The duration of the period of ingestion of fresh yeast affected the speed with which the previous level of urinary output of thiamine was again attained when yeast was removed from the diet, indicating a progressive depletion of body stores from ingestion of fresh yeast. Bakers' yeast killed by commercial drying processes or by treatment in boiling water released its thiamine for absorption and offered no interference to absorption of food thiamine. In these authors' opinion, live yeast cells in the digestive tract compete with the host for the thiamine that is present. FREDEEN, Kansas City, Mo.

THE EFFECT OF INGESTED MINERAL OIL IN PLASMA CAROTENE AND VITAMIN A. BENJAMIN ALEXANDER, EVELYN LORENZEN, RICHARD HOFFMANN and ARLENE GARFINKEL, Proc. Soc. Exper. Biol. & Med. **65**:275 (June) 1947.

Twenty-two human subjects were given liquid petrolatum or salad dressing composed of 83 per cent liquid petrolatum for three to eight weeks, and the plasma carotene and vitamin A levels were determined periodically. Three additional patients received no liquid petrolatum, but the diet was unrestricted in all 25 subjects. It was observed that the administration of liquid petrolatum caused a definite reduction (about 50 per cent) in the plasma carotene concentration, whereas no change occurred in the vitamin A levels. The effect is probably due to the solution of carotene in the liquid petrolatum in the intestinal tract, hence the failure of absorption. HANSEN, Galveston, Texas.

INTRODUCTION TO VITAMIN THERAPY. G. MOURIQUAND, Pédiatrie **36**:17 (Jan.-Feb.) 1947.

In this brief introduction, the author classifies vitamin therapy into three fields: (1) dietary deficiencies which, if recognized, will respond to the administration of the missing vitamin; (2) digestive disturbances, either primary (vomiting, diarrhea or intestinal infection) or secondary (avitaminosis B and C in experimental animals; sprue and celiac disease in human beings), and (3) internal diseases causing a faulty utilization of vitamins or absence of transformation of their precursors. Hepatic damage will prevent proper transformation of carotene into vitamin A and of prothrombin into vitamin K; insufficient bile secretion hinders the absorption of fat-soluble vitamins (vitamins A, D and K). Endocrine disturbances can interfere with vitamin metabolism: hyperthyroidism interferes with vitamin A metabolism and hyperparathyroidism with that of vitamin D. The cardiovascular, respiratory and nervous systems influence and are influenced by vitamins (myocardium and vitamin B_1; lungs and vitamin A; nervous system and vitamin B_1). The bone structure and calcium metabolism are in close interrelationship to vitamin D.

Finally, infections and toxic conditions may cause the body to require larger amounts of vitamins because of a certain "vitamin refusal" of the diseased organism.

GLASER, Chicago.

NICOTINAMIDE AND PHOSPHORUS IN THE BLOOD. V. D. BORI and S. STEFFENONI, Policlinico inf. **15**:331 (July) 1947.

The authors measured the blood phosphorus and nicotinamide content in 14 children. Most of them had rickets. The authors observed that in subjects having a low level of phosphorus, there is also a low level of nicotinamide. They advance the hypothesis that nicotinamide might in some way act on the metabolism of phosphorus and have an influence in the pathogenesis of rickets.

FROM THE AUTHORS' SUMMARY.

Prematurity and Congenital Deformities

THE RATIONALE OF BLOWING EXERCISES FOR PATIENTS WITH REPAIRED CLEFT PALATES. CLAUDE E. KANTERN, J. Speech Disorders **12**:281 (Sept.) 1947.

Blowing exercises in work with the patient with cleft palate are given early so that the patient will learn better voluntary control and hence improve the use of the palatal muscles and so that there will be an actual strengthening and development of the muscles themselves. The first of these assumptions seems well founded. The second is logical but difficult to prove. Blowing exercises are valuable only when they motivate the patient's effort to make the utmost use of the muscles involved. Presurgical training in this matter is useful. At least within a month following repairs, blowing exercises should be begun. The first blowing exercises should be easy because the violence of the breathing exercise is no criterion of its value. Blowing a balloon should be reserved until good closure is made by the patient. Grimaces and contractions of the nares should be avoided. Blowing exercises have given their maximum benefit when the patient has full awareness of the concept of oral direction of the air stream, when he is able with ease to contract and relax the muscles of the palate voluntarily, and when he has attained the maximum degree of closure of the opening into the nasopharynx in terms of the structural and neuromuscular limitations of the soft palate and surrounding structures. The only valid criterion of palatal efficiency is the amount of air escaping through the nose in relation to the amount emitted orally. It is important that the total amount of air be expelled and the length of exhalation be kept approximately constant, since in blowing against pressure the proportion of air escaping through the nose tends to rise as the breath pressure increases. The spirometer is useful, too, in measuring this efficiency. Blowing exercises themselves are useless without other training in the correction of speech. Blowing exercises should not be given during periods of infection of the nose and throat. Blowing exercises should not be given patients in whom the palate is so inadequate that there is no possibility of improvement. The amount of nasality in speech is not directly related to the amount of nasal flow of air. Some patients with complete closure of the obturator are extremely nasal, while patients with considerable opening have little nasality. Some patients acquire extensive pharyngeal movements with little improvement in speech; others do not develop these spontaneously. The questions of pharyngeal movements have not been satisfactorily answered in the literature. PALMER, Wichita, Kan.

PREMATURITY—AN ORIENTATION. ETHEL C. DUNHAM, New Orleans M. & S. J. **100**:119 (Sept.) 1947.

Dr. Dunham presents a brief discussion pointing out the high mortality from premature birth and the chief causes thereof, as well as the chances for reducing this mortality and the prognosis for future development of premature infants. She emphasizes the downward trend in premature death over a period of ten years from 1934 to 1944 and discusses the possibility of reducing deaths by better antenatal, neonatal and postnatal care. Stress is laid on the importance of preventing premature birth by proper prenatal care. McGUIGAN, Evanston, Ill.

ARACHNODACTYLY WITH AMYOPLASIA CONGENITA. H. M. M. MACKAY, Proc. Roy. Soc. Med. **39**:696 (Sept.) 1946.

The baby was seen at 10 days of age and had not seemed normal since birth. The arms were flexed at the elbow joints. The knees were flexed, with decided limitations of extension. The hands were large with long, spidery fingers and the feet were long and thin. There was pronounced kyphosis in the lower thoracic and lumbar regions. No abnormalities in the eyes or heart were observed. The electrical reactions of the muscles were normal in the biceps, triceps and hamstring muscles, but no response to faradism or galvanism was elicited in either quadriceps muscle. The fixation of the elbows and knees in flexion at birth and the thinness of the muscle groups of the limbs are usually noted in cases of amyoplasia congenita.

WILLIAMSON, New Orleans.

A DICEPHALIC MONSTER COMPLICATING LABOR. C. RHODES-HARRISON, South African M. J. **21**:744 (Oct. 11) 1947.

A case of fetal dystocia is described in which roentgenograms revealed a dicephalic monster. Cesarean section was performed, the two heads amputated and the remainder of the body drawn out through the vagina. The fetus had two perfect heads, right and left arms, a third arm with two humeri, two scapulas, two clavicles, three forearm bones and a hand made up of two hands fused along the inner border, with a common little finger. The thorax contained two hearts and two sets of lungs. Below the diaphragm the body was normal.

McGUIGAN, Evanston, Ill.

CONGENITAL DEFORMITIES OF THE FOREARM. A. VAN DER SAR, Nederl. tijdschr. v. geneesk. **91**:313 (Feb. 8) 1947.

Two cases of nonfamilial, bilateral radioulnar synostosis in Negro children are reported. In a third case there was congenital aplasia of the ulna, together with absence of the fourth and fifth fingers. The thoracic wall was incompletely developed; there was a cervical rib, and the second and third ribs were only partially developed. In this patient a familial disposition was demonstrable, together with or influenced by sickle cell anemia.

VAN CREVELD, Amsterdam, Netherlands.

Newborn

CONGENITAL ULCER OF THE SKIN AND BONE OF THE SKULL (OMBRÉDANNE'S DISEASE). C. MASSERONI, Lattante **18**:169 (March) 1947.

A 7 day old infant was admitted to the hospital with an ulceration 3 cm. in diameter at the tip of the occiput and involving the skin and bone. This lesion of intrauterine origin healed in approximately forty-five days. HIGGINS, Boston.

FREQUENCY OF RH FACTOR AMONG THE ITALIAN POPULATION. P. BUONOCORE and M. AMATO, Pediatria **55**:196 (April-June) 1947.

Of a group of 563 persons studied, 85.8 per cent were Rh positive and 14.2 per cent were Rh negative. Of the men 8.1 per cent and of the women 19.8 per cent were Rh negative. Of those in blood group O 15.4 per cent, of those in blood group A 14.8 per cent, of those in blood group B 7.8 per cent and of those in blood group AB 10 per cent were Rh negative. These percentages are about the same as those obtained by American and European workers among other peoples of the white race.

HIGGINS, Boston.

SIGNIFICANCE OF WELTMANN AND TAKATA-ARA REACTIONS IN THE BLOOD SERUM OF NEWBORN INFANTS. D. ORIGLIA and U. VIGNOLO-LUTATI, Pediat. d. med. prat. **22**:1 (Jan.) 1947.

Samples of the blood serum of 55 normal newborn infants were obtained from the umbilical cord and tested by the methods of Weltmann, Weltmann and Havas and Takata and Ara. In the Weltmann tests, flocculation occurred in the weakest concentration in 49 samples and in the next to the weakest in 6. In the Takata-Ara test, 38 samples showed a 4 plus reaction, 12 a 3 plus reaction and 5 a 2 plus reaction. The reactions were the same in the blood serums obtained from the same infants at the age of 1 week. The tests seem to indicate the presence of gamma globulin, which is stated by the authors to contain the antibodies of the blood. This is perhaps the explanation of high neonatal immunity.

HIGGINS, Boston.

HEMOLYTIC DISEASE OF THE NEWBORN AND THE IMPORTANCE OF RH FACTORS. KURT O. WEBER, Ann. Pædiat. **169**:1 (July) 1947.

Along with the description of 7 cases of erythroblastosis fetalis, observed in the course of several years, the discovery, development and increasing importance of the problems involving the Rh factor are discussed, as well as their essential bearing on therapy and clinical management. In particular, all the theories and knowledge which existed up to the writing of this paper are examined and compiled. The theories and attempts at explanation in existence before the discovery of the Rh factor are also mentioned.

Experiences derived from the author's own observations and from facts given in the literature are extensively discussed, and the principles which are important for treatment are explained. The prophylactic treatment with liver extract which, as experience has shown, is so beneficial is stressed.

FROM THE AUTHOR'S ABSTRACT.

Acute Contagious Diseases

HISTOPATHOLOGIC CHANGES ASSOCIATED WITH HUMAN POLIOMYELITIS. I. MARK SCHEINKER, Arch. Neurol. & Psychiat. **57**:565-577 (May) 1947.

The author presents pathologic evidence to support the idea that acute anterior poliomyelitis is not restricted to the anterior horns of the spinal cord. The medulla, pons, midbrain, hypothalamus and cerebellum were involved "to a great extent" in every case studied. The view is also expressed that the degenerative neuronal changes and the inflammatory reaction are independent phenomena.

The pronounced concentration of the inflammatory and degenerative tissue reactions in the region of the vagal nuclei observed in all the cases provides additional suggestive evidence of the possible spread of the virus from the intestine into the central nervous system by way of the afferent and efferent pathways of the vagus nerve (Sabin).

BEVERLY, Oak Park, Ill.

DIPHTHERIA IN THE PEDIATRIC CLINIC OF FLORENCE, ITALY, 1941 TO 1943. TORQUATO LUIGI CALÓ, Riv. clin. pediat. **45**:290 (May) 1947.

The author compiled statistics on 672 children with diphtheria admitted to the Children's Hospital of Florence, Italy, between 1941 and 1943, comparing these with the previous statistics of the hospital. He considers in particular the complications, bronchopneumonia especially, the sequelae, the prognosis and the malignant forms in relation to modern therapy. After brief presentation of the more important etiologic and pathogenetic views, he discusses the results of his research and confirms the efficacy of antidiphtheria serum therapy and of antipneumonia serum

prophylaxis. He observes that the course of the epidemic appeared serious during this period, as the mortality increased even in uncomplicated cases. He notes that in the cases complicated by bronchopneumonia the mortality was greatly decreased. This diminution was, in his opinion, probably due to sulfanilamide therapy, which he considers justified even for malignant cases.

FROM THE AUTHOR'S SUMMARY.

POLIOMYELITIS AND SCURVY. FERNANDO LOPEZ CLARES, LYDIA G. DE MONTALVO and EUGENIO TOUSSAINT, Bol. méd. d. hos. inf. Mexico **4**:332 (May-June) 1947.

A 33 month old girl was admitted to the contagious disease service of the hospital with the diagnosis of poliomyelitis. She was malnourished and had paralysis of both lower limbs, which were flexed and painful.

The clinic and the laboratory discarded the possibilities of rickets, spina bifida occulta and congenital dislocation of the hip. The reason for the elimination of this last disease was that the patient had scoliosis.

The roentgenograms of the bones showed scorbutic lesions in the costochondral joints, in the epiphysis and diaphysis of the femurs and tibias and in the points of ossification and subperiosteal effusion in the right tibia.

The treatment with a synthetic vitamin C preparation and orange juice cured the patient of her osseous scurvy in two months. The pain disappeared completely, leaving only a flaccid paralysis of the left lower limb that affected the quadriceps and adductor muscles. This was caused by the poliomyelitis. The right lower limb was normal.

The scurvy was caused by the lack of vitamin C in the food which the child had eaten throughout her life. The fact that the patient's 14 month old brother contracted poliomyelitis two months later may be mentioned as an important epidemiologic datum.

The combination of scurvy and poliomyelitis is a rarity which we have not found described in the medical literature. On the other hand, the transient paralysis seen in scurvy must be differentiated when the diagnosis of poliomyelitis is made.

It is interesting to note the infrequency of any signs of scurvy in the bones of the children of this region, when so many varieties of other avitaminoses are frequently found, especially those caused by lack of vitamins of the B complex. We believe these lesions should be looked for more carefully. (Two cases of scurvy combined with rickets were published in the "Memorias del Primer Congreso Mexicana de Pediatría" in 1938.) It is also interesting to note the lack of other scorbutic manifestations in the present patient.

FROM THE AUTHORS' SUMMARY.

PSEUDOINHIBITION AS A RESULT OF PARALLERGIC REACTION IN MEASLES. C. PAPP, Paediat. danub. **1**:292 (May) 1947.

Allergic reactions undergo a change during the incubation period of measles. The response to a new antigen given during this time is either hastened or immediate. Intradermal administration of foreign proteins, as serum of ferrets or guinea pigs or extracts of bovine placenta, is followed by an eruption at the site of the injection, although the patients were previously not sensitized with these substances. When the foreign protein is injected five days before the eruption of measles starts, the serum exanthem will appear together with that of the measles. On the other hand, when the injection is given during the last days of the incubation period, that is, 24 to 72 hours before the appearance of the rash of measles, an immediate response will be obtained, the serum exanthem appearing within 24

hours. This exanthem fades in another 24 hours and a pale circumscribed area remains, imitating the usual phenomenon of inhibition (pseudoinhibition).

The reaction is not a specific one and is not due to antitoxins present in the blood of the animals. In order to prove this, the experiment was repeated with the serum of an inoculated ferret. The administration of this did not give rise to a serum exanthem and did not inhibit the efflorescence of the measles rash, which appeared at the site of the injection just as it appeared elsewhere on the body.

This experiment, apart from showing that there are no measles antitoxins in the blood of ferrets, proves that the inhibition phenomenon of Debré is not reliable in demonstrating antibodies in the serum of animals.

An additional significance of the experiments is that they call attention to the altered allergic state of patients in the last days of incubation and the prodromal period. The parenteral administration of a new antigen in this period may involve some risks. It is presumable that the unstable and unsatisfactory results of vaccinations with serum of sheep, as recommended by Degkwitz, were due to such parallergic reactions.

FROM THE AUTHOR'S SUMMARY.

ETIOLOGIC ANALYSIS OF CASES OF "PERTUSSIS BRAIN." K. FRANK, Paediat. danub. **1**:332 (June) 1947.

The endotoxin of Hemophilus pertussis and the hemodynamic effect of whooping cough frequently cause convulsions in infants and little children.

Thirty-eight cases of whooping cough with involvement of the nervous system (cases hitherto termed "pertussis brain") were analyzed with regard to their precise causation. The underlying causes of the convulsions were discovered to be intracranial hemorrhages, tetany, infectious serous meningitis, meningism, encephalitis or encephalosis. The differentiation of encephalitic pictures is of great importance in order that immediate, adequate treatment be started.

The nervous complications are more frequent when the underlying disease is complicated by infections of the respiratory tract or other infections. The gravest forms develop almost always in cases of pertussis pneumonia. Vitamin D must be immediately given to infants and young children with rickets if they contract whooping cough.

Cases are mentioned that were termed encephaloses, on the basis of analyses of the cerebrospinal fluid. This clinical pattern corresponds to the encephalopathy of the pathologists. Lumbar puncture is recommended when the least sign of an involvement of the central nervous system appears. The analysis of the cerebrospinal fluid is of great help in determining an adequate treatment.

FROM THE AUTHOR'S SUMMARY.

Acute Infectious Diseases

TWO FORMS OF CRYPTORCHISM. BENNO GRÜNFELDER and WALTER LASCH, Ann. pædiat. **167**:28 (July) 1946.

There are two types of cryptorchism: an anomaly of descent without other anomalies of sexual organs, but with normal function of adrenal glands and normal development of the olfactory center, and congenital agenesis, hypoplasia or aplasia of the testes with coexisting anomalies of sexual organs, such as hypospadias, atrophy of the scrotum, contracture of the raphe scroti and hypoplasia of the penis, while at the same time there is absence of the sense of smell and possibly hypoplasia or aplasia of the adrenal glands.

In order to be able to differentiate these two types of cryptorchism, diagnostic methods for early childhood should be evolved which either confirm or refute the presence of an intact adrenal function and olfactory center. Congenital cryptor-

chism is not necessarily combined with both the anomaly of the olfactory region and that of the adrenal glands; one or the other may be predominant.

FROM THE AUTHORS' SUMMARY.

PERINEPHRITIS WITH AND WITHOUT OPERATION. W. B. J. GERRITS and H. J. JONGEPIER, Ann. pædiat. **167**:44 (July) 1946.

Two cases of perinephritis are described, in the first of which there was surgical intervention after the formation of an abscess, while in the other treatment was exclusively with penicillin. In the latter case, diagnosis was established with the help of respiration pyelography, a roentgenologic method which is still used too little for diagnosing diseases in the region of the kidney.

FROM THE AUTHORS' SUMMARY.

Chronic Infectious Diseases

EARLY CONGENITAL SYPHILIS: TREATMENT OF TWO HUNDRED AND FIFTY-TWO PATIENTS WITH PENICILLIN. R. V. PLATOU, ALLAN J. HILL JR., NORMAN R. INGRAHAM, MARY S. GOODWIN, ERLE E. WILKINSON, ARILD E. HANSEN and ALBERT HEYMAN, J. A. M. A. **133**:10 (Jan. 4) 1947.

This is the report of the treatment of 252 congenitally syphilitic infants with sodium penicillin in five university medical centers under the Committee on Medical Research of the Office of Scientific Research and Development.

Satisfactory results for a single course of penicillin administered over a period of seven and one half to fifteen days were obtained in 73 per cent; in 9.1 per cent the resulting condition was unsatisfactory and in 17.9 per cent it is still classified as uncertain. Dosage schedules using more than 40,000 units of penicillin per kilogram of body weight gave better results. Treatment of the infant remains more important than treatment of its syphilis. The following broad suggestions for therapy are offered:

1. Young syphilitic infants should receive a total dosage of at least 100,000 units per kilogram of body weight.

2. This amount should be divided into approximately one hundred and twenty equal intramuscular injections given over twelve to fifteen days.

3. These injections should be given at intervals of no longer than three hours around the clock.

BAIRD, Wauwatosa, Wis.

TREATMENT OF TUBERCULOUS MENINGITIS WITH STREPTOMYCIN, SULFONES AND VITAMIN A. CESARE COCCHI and GAETANO PASQUINUCCI, Riv. clin. pediat. **45**:193 (April) 1947.

Twenty-eight patients with tuberculous meningitis were treated or are still under treatment. Of these, 7 died, but they, in the great majority, were in a serious condition in the last phase of the illness. All patients with tuberculous meningitis received in the clinic were treated without exception.

Of the 20 patients who survived, 1 is still in a serious condition; the others are, for the greater part, clinically cured or approaching clinical cure. The sooner treatment is started the quicker the improvement and the clinical recovery. Tuberculous meningitis, contrary to what had been considered certain until now, is a disease that can be treated and cured. In our patients, up to the present, no important posthumous effects have been noted. In those series treated only with streptomycin, the results were much less favorable than the ones obtained in our series.

The introduction of streptomycin by lumbar puncture is essential. The doses of streptomycin which seemed to us most efficacious were well below those used by American authors.

Streptomycin must be prudently used, especially in lumbar puncture, because it is not harmless and has caused some reactions, the importance of which we cannot yet judge completely. The doses which seemed to us the most suitable are 25 to 50 mg. by lumbar punctures (which certainly give active results and are harmless) and 300 mg. *pro die* in six doses intramuscularly.

Intensive treatment with vitamin A intramuscularly and the use of vitamin D_2 with a certain caution have seemed important to us.

The subacute, benign and asymptomatic course of the residual meningeal reaction in patients convalescent from tuberculous meningitis remains to be studied.

FROM THE AUTHORS' SUMMARY.

SIGNIFICANCE OF BRONCHIAL PERFORATIONS IN TUBERCULOSIS OF ENDOTHORACIC LYMPH NODES. O. GÖRGÉNYI-GÖTTCHE and D. KASSAY, Ann. pædiat. **168**:311 (June) 1947.

The perforation of tuberculous material into the bronchial tree was observed eighteen times with the aid of the bronchoscope and eight times during autopsy. The perforation was observed in 47.1 per cent of the cases, in 17.6 per cent in two places. The sequelae of the perforation are not always as serious as have been assumed to date. In this way, the caseating lymph nodes empty their contents, which are then evacuated by coughing. The perforation into the bronchi occurs four to six months after the primary complex has become manifest; expiratory sighing and grunting, wheezing and bitonal cough are its signs. In 61.6 per cent of the cases the elevation in temperature is produced by atelectatic pneumonia or bronchogenic dissemination. Among the roentgenologic signs the Holzknecht-Jacobson phenomenon is important. Each case of valvular stenosis forms an indication for bronchoscopy, a procedure which is without danger in infancy and childhood.

FROM THE AUTHORS' SUMMARY.

Diseases of Blood, Heart and Blood Vessels and Spleen

VON GIERKE'S DISEASE (GLYCOGENOSIS). T. TWISTINGTON HIGGINS, Proc. Roy. Soc. Med. **39**:587 (Aug.) 1946.

A case of glycogenosis (von Gierke's disease) is reported in a child 2 years old.

WILLIAMSON, New Orleans.

NEUROANEMIC SYNDROME IN A CHILD WITH FAMILIAL HEMOLYTIC ICTERUS. FRANCESCO PECORELLA, Riv. di clin. pediat. **44**:690 (Nov.) 1946.

The author describes spasmodic paraplegia (Riesen-Russel syndrome) occurring in a girl 9 years old with familial hemolytic icterus (Minkowski-Chauffard).

From a pathogenic point of view, the existence of incomplete interdependence was shown between the hematic syndrome and the nervous one. On the basis of actual scientific knowledge, the hypothesis was advanced that the hematic and nervous alterations are determined by different pathogenic factors from a single cause.

FROM THE AUTHOR'S SUMMARY.

SERUM IRON LEVELS IN CHILDREN WITH FAMILIAL ERYTHROBLASTIC (COOLEY'S) ANEMIA. MAURO AMATO, Riv. di clin. pediat. **44**:711 (Nov.) 1946.

The author studied the behavior of serum iron in 6 children with familial erythroblastic (Cooley's) anemia. In 5 of them the values proved throughout to be higher than normal and in only 1 was the level lower than normal.

Considering the hypochromic type of this anemia and having observed only slight elimination of bilinogen in these patients, the author is inclined to ascribe the

increase in serum iron values to an inadequate utilization of the metal by the erythropoietic marrow centers. The author draws attention to the possibility that the functional disturbance of marrow activity with respect to hemoglobin synthesis may represent an important and hitherto insufficiently valued element in the pathogenesis of familial erythroblastic anemia.

He points out the analogy between the data obtained in these cases of anemia and those obtained by Perosa in cases of hemolytic jaundice with increased osmotic resistance.

FROM THE AUTHOR'S SUMMARY.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

HEPATOMEGALY, DWARFISM AND OBESITY IN CHILDHOOD DIABETES. P. MAURIAC, Presse méd. **54**:826 (Dec. 14) 1946.

A diabetic girl was seen first at the age of 4 years. She became obese and as her liver enlarged her growth ceased. The liver reached the iliac crest and remained this size until severe acidosis occurred at the age of 15 years. During this crisis, the liver shrank in size until it was only 2 fingerbreadths below the costal margin. Enlargement gradually recurred, and, when she was 16½ years old, the liver again was huge. The patient had suddenly grown 6 cm. taller but showed no signs of maturing. At that time, another severe acidosis developed with coma, requiring 120 units of insulin a day. The liver again returned to normal size and has not enlarged since. Secondary sex characteristics then began to appear, and she matured a year later. She still is small and obese, and the diabetes remains intractable. Mauriac states his opinion that the anterior lobe of the pituitary is at fault in this syndrome, with the pancreas and liver secondarily involved.

DAFFINEE, Melrose, Mass.

TRICHOBEZOAR IN CHILDHOOD. PAOLO STURLESE, Riv. clin. pediat. **45**:257 (May) 1947.

After a discussion of the bezoars and of the pathologic significance of these formations, the author reports a case of a 9 year old child. After ascertaining the clinical and roentgenologic diagnosis, he successfully carried out the operation. The removed trichobezoar weighed 285 Gm., was 28 cm. long and had a maximum circumference of 16 cm.

FROM THE AUTHOR'S SUMMARY.

HYPERTROPHIC PYLORIC STENOSIS. FERNANDO OSORIO and JESÚS LOZOYA S., Bol. méd. d. hosp. inf. **4**:311 (May-June) 1947.

Congenital hypertrophic pyloric stenosis is a grave disease that may be fatal unless surgical intervention is opportune. The diagnosis is based on the occurrence of projectile vomiting and wasting and the palpation of peristaltic waves. When doubt exists, the roentgenograms clarify the diagnosis. The disease is not to be considered to demand immediate urgency in treatment.

The operation must be preceded by improvement in the condition of the patient with all the therapeutic means within reach. Surgical intervention, using the Ramstedt-Fredet-Robertson technic, is the best treatment. The operation must be done gently with minimal manipulation, incision of the pyloric muscle as close as possible to the convexity, complete discission of the muscular tumor, perfect hemostasis and avoidance of a duodenal performation.

Good postoperative care is essential. Feeding must be renewed early in small amounts, to progress quickly to normal amounts. Complications should be prevented, but, if they arise, the surgeon must combat them with all the means at his disposal.

One should always remember that "there is a greater risk in waiting than in operating."

FROM THE AUTHORS' SUMMARY.

Diseases of Nose, Throat and Ear

SEX DIFFERENCES IN RELATION TO STUTTERING: PART II. HILDRED SCHUELL, J. Speech Disorders **12**:23, 1947.

Three studies were made of children in South Bend, Ind., relative to sex differences in parental attitudes toward the children's behavior. The children in study I were from elementary school classes in creative dramatics and junior high school sections of speech taught by the author. Questions relative to parental punishment and praise were written on the board and papers were written by the children. More girls than boys reported that they were punished by their mothers for not helping with housework, by their fathers for carelessness, procrastination and impertinence. More girls than boys reported that they were praised by their mothers for helping with housework, for good work at school and musical accomplishments and were praised by their fathers for good work at school and for helping their mothers. More boys than girls reported that they were punished by their mothers for staying out late, quarreling and personal appearance. More boys were punished by their fathers for neglecting assigned tasks and reported receiving no praise from either father or mother. Boys tended to be punished more severely than girls. These data seem to imply that girls feel more security than boys in family, school and social situations.

Study II concerned the same school population six months later, thus representing a different group of children, and was done on the basis of a written questionnaire. More boys than girls received punishment and reported punishment by their mothers for staying out late, fighting and being disorderly. More boys than girls reported punishment from their fathers for all items except noise. The hypothesis is offered that these significant differences constitute a real sex difference in the amount and degree of child-parent conflict.

This particular study confirms the general findings of the preliminary study, to the effect that boys experience more conflict and more insecurity than girls. This is indicated by the amount of punishment and praise given by parents and the children's attitudes toward school and relationships with other children.

Study III was an exploratory study designed to discover sex differences in parent-child relationships at the preschool level. The subjects were 28 children between the ages of 26 and 53 months, equally divided as to sex, and of a superior social and economic status. At least one parent of each child was interviewed, in most cases the mother. The parents were asked to keep a record sheet for two weeks recording occurrences of disturbances in eating, bed, nap, bath, dressing and toilet. More girls than boys were reported to be punished for being destructive and noisy and for items not specified. While no statistical significance can be attached to the third study, the data tend to suggest that if a more comprehensive study of child behavior and parental attitudes was made at this age level similar differences as to sex would be reported.

These studies tend, in the writer's judgment, to support the hypothesis that stuttering is a semontogenic and diagnostic disorder, arising when the repetitions, hesitations and other inadequacies characteristic of the speech of young children are diagnosed as stuttering and this evaluation is reacted to, or interiorized, by the child. It is hypothesized that stuttering and sex differences in the incidence of stuttering can be accounted for by a combination of psychologically determined factors and responses to culturally determined stimulus-complexes which are different for girls and boys and men and women. PALMER, Wichita, Kan.

A GROUP PURE TONE HEARING TEST. SCOTT N. REGER and HAYES A. NEWBY, J. Speech Disorders **12**:61, 1947.

Forty ear phones were connected to the output of a pure tone audiometer, the oscillator circuit of which was suppressed or released, according to a predeter-

mined sound stimulus pattern, by a mechanically operated tone interrupter, while an attention-focusing light was illuminated. The mechanism to illuminate the attention light consisted of five bakelite® disks 4 inches (10 cm.) in diameter and ¼ inch (0.6 cm.) thick. The disks were rotated 6 revolutions per minute, and the one to four projecting teeth on their perimeters actuated microswitches.

The disk associated with the 60 watt attention light illuminated the bulb 0.5 second before the first tone of the sound pattern was produced. While the light was off, the operator turned a selector switch to select any one of the desired frequency and intensity levels. The operator followed a key which showed him the proper intensity level settings and the number of interruptions for every square of the test blank. The top square of each column represented a tone of 40 decibels above the normal threshold. Proceeding down each column, the tone was presented successively 40, 30, 20, 15, 10 and 5 decibels above normal. Frequencies tested were at 256, 1,024, 2,048 and 4,096 cycles.

Preliminary experimentation was undertaken with a group pure tone test used in conjunction with ten permoflux® dynamic ear phones instead of the forty Western Electric ear phones. With the permoflux® phones it was possible to test the acuity through 8,192 cycles. Thirty additional permoflux® phones will be obtained in the future. On the basis of this group test all entering students of the State University of Iowa with serious losses at any of the four frequencies were screened out for thorough examination. Approximately 2,400 pupils in the Iowa City public school system were tested during the 1946-1947 school year.

PALMER, Wichita, Kan.

A PRELIMINARY INVESTIGATION IN THE TESTING OF LIP READING ACHIEVEMENT. GLADYS REID, J. Speech Disorders **12**:77, 1947.

Sixty-two girls from the Lexington School for the Deaf in New York city and 37 girls from the State School for the Deaf, at Delavan, Wis., were selected for a lip-reading test on motion picture film. Each test consisted of (1) a series of 17 vowels and diphthongs, (2) a series of 11 consonants, (3) a series of 10 unrelated sentences, (4) a series of related sentences telling a story and (5) a short story at the end of which were four questions the subjects were to answer. The children from the Lexington School were tested in groups of about 20. At the school for the deaf in Wisconsin, the test was given to the entire group at the same time.

The results of this study indicate low correlations approaching 0 between lip-reading ability on the test used and other factors. From these results, it is reasonable to conclude that lip-reading ability is not quantitatively correlated with, and cannot be predicted from, the length of training in lip reading, mental age, intelligence quotient or grade status. However, it must also be considered that in this study only one factor in the total lip-reading situation, namely, articulation, was isolated and tested.

PALMER, Wichita, Kan.

Nervous Diseases

THE TREATMENT OF MENINGITIS DUE TO HAEMOPHILUS INFLUENZAE WITH STREPTOMYCIN. LOUIS WEINSTEIN, New England J. Med. **235**:101 (July 25) 1946.

Nine patients with purulent meningitis, due to type B Hemophilus influenzae in 7 and to an untypable strain in 2, were treated with streptomycin, with complete recovery in 7 cases. The drug was given intramuscularly in doses ranging from 15,000 to 125,000 units every three hours and intrathecally in amounts varying from 10,000 to 25,000 units every twenty-four hours. Two of the 9 patients with influenzal meningitis treated with streptomycin died. One showed complete absence

of response to the antibiotic agent. The other died of an intercurrent bronchopneumonia due to Staphylococcus aureus, which was not affected by penicillin.

The blood and spinal fluid were cleared of the causative organisms in from twenty-four to forty-eight hours in all cases except the 2 due to atypical strains. No relapses or sequelae of the influenzal meningitis were observed in any of the recovered patients over a period of from six to ten weeks after the cessation of streptomycin treatment. No toxic reactions attributable to streptomycin were observed in the nervous, hematopoietic or urinary systems.

Infection with Staph. aureus developed in 2 of the patients receiving streptomycin—meningitis in 1 patient and bronchopneumonia in the other—after they had been completely free of H. influenzae in both the spinal fluid and blood for several days and were apparently recovering clinically. Bacteremia was present in both.

FROM THE AUTHOR'S SUMMARY.

FUNCTIONAL REEDUCATION OF THE PARAPLEGIC PATIENT WITH COMPLETE SECTION OF THE CORD. ALFONSO MONTAGNE, Rev. d. Hosp. del Niño **8**:201 (Sept.-Dec.) 1946.

Methods other than operative by which the paraplegic patient may be helped considerably are reviewed. Patience, ingenuity and the art of the physician combine in an important way to aid the patient to obtain some degree of independence. The proper selection of patients, the basic knowledge of muscular function and the intelligent help of auxiliary personnel facilitate in the recuperation of those patients formerly considered beyond help. KEITH, Rochester, Minn.

MENINGORADICULITIS AND THE SYNDROME OF GUILLAIN-BARRÉ AND STROHL. A. LAMENZA and S. SANTYAN Y VELASCO, Riv. clin. pediat. **44**:585 (Oct.) 1946.

From the observation of 4 cases in children, acute meningoradiculitis is discussed, especially in relation to the Guillain-Barré and Strohl syndrome. The various data, the symptoms and the clinical course of these cases are analyzed, from which analysis a particular nosologic entity of the clinical syndrome as described by Belgian authors appears doubtful. These personal observations, and especially those in 1 case, offer the basis for clinical investigation especially in regard to acute anterior poliomyelitis (Heine-Medin disease), which may often show meningoradicular symptoms. One cannot, therefore, exclude the possibility that some meningoradiculitis may be connected with a nonaxial localization of the poliomyelitis virus. FROM THE AUTHORS' SUMMARY.

PURULENT MENINGITIDES CAUSED BY POLYMORPHOUS HEMOPHILUS BACTERIA (HEMOPHILUS INFLUENZAE?). LELIO NASSI, Riv. clin. pediat. **44**:649 (Nov.) 1946.

The author describes his clinical, therapeutic and bacteriologic observations on 23 cases of purulent meningitis caused by polymorphous hemophilus bacteria. With the study of isolated organisms through cultures of some months' duration, he was able to observe a change of the bacillary or filament forms into typical forms of cocci, often coupled and sometimes resembling meningococci.

These morphologic changes, observed not only in the cultures but also in the spinal fluid, sometimes showed themselves reversible. Nassi states his belief also that through further research (on the biochemical activity of the bacteria and their pathogenic properties toward laboratory animals) these observations, if not contrary to the hypothesis that they are Hemophilus influenzae (Pfeiffer's bacillus), at least show a new aspect of these organisms. To this must be added the histopathologic findings in the meninges, where the presence of histoid reactions with giant cells resembles the lesions from actinomyces. The author is of the opinion that the problem of the more exact classification of these bacteria is still open to discussion.

From a clinical point of view are mentioned the diagnostic difficulties and those of prognosis, which are due to the polymorphous aspect of these germs and their occasional absence from the spinal fluid even in the acute period of meningitis. Even the so-called meningitis caused by many types of bacteria might originate from these polymorphous forms.

The author reports 4 cases of recovery of 10, with penicillin treatment. He suggests as necessary the intraspinal introduction of 10,000 to 20,000 units of penicillin twice a day, together with intramuscular injections, in conjunction with the normal sulfonamide therapy.

He considers it necessary that therapy be perfected, with adaptation (either with the use of the various sulfonamide drugs or other antibiotic substances or with the use of specific serums or blood transfusions) to the various phases of development of the bacteria in the spinal fluid, so that the prognosis of these types of meningitis can be further improved. FROM THE AUTHOR'S SUMMARY.

INFILTRATING ASTROBLASTOMA IN CORPORA QUADRIGEMINA AND QUADRIGEMINAL REGION. J. M. MACERA, J. A. GHERSI and J. C. OYHENART, Arch. argent. de pediat. **26**:343 (Nov.) 1946.

A case of infiltrating astroblastoma of the cerebral peduncles, in which the epicenter of the tumor was in the corpora quadrigemina and the quadrigeminal region, is reported. The diagnosis was difficult because of the existence of ocular symptoms in an old neurologic clinical picture, probably due to postencephalitic lesions, in the place in which the astroblastoma developed.

Some facts which corroborate the contention that lumbar punctures should not be made for patients with intracranial hypertension and papilledema are pointed out.

ROJAS, Boston.

PNEUMOCOCCIC MENINGITIS IN THE NEWBORN. G. GONZALES AGUIRRE and J. J. REBOIRAS, Arch. argent. de pediat. **26**:416 (Dec.) 1946.

Nine cases of pneumococcic meningitis in the newborn are reported. In 5 of them the patients were treated with sulfonamide drugs, and in 4, with a combination of penicillin and sulfonamide compounds. Three patients of the first group died. One was cured but had the sequelae of hydrocephalus and amaurosis, and the other was cured completely. Of the patients treated with penicillin and sulfonamide drugs, two were cured completely.

The method of treatment followed by the authors was that outlined by Cairn and Smith, with the difference that the authors gave 5 per cent sulfamerazine intravenously, when possible. ROJAS, Boston.

INFANTILE EPILEPSY. M. GOLDBERGER, Orvosok lapja **3**:450 (April 6) 1947.

Infantile epilepsy affects the almost completely developed subcortex and the yet undeveloped, immature cortex. The author discusses the peculiarities of the disease in the light of this fact. In a group with genuine epilepsy at the period of increased permeability of the cerebral membranes, fits which were caused by slight injuries can often be observed. Recent tests limit genuine epilepsy to a narrow field. The author's observations offer a guide to determining which patients should have antiepileptic medicaments and treatment.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

NEVOID AMENTIA (STURGE-WEBER DISEASE) IN CHILDHOOD. VLADIMIR KLUSKA, Pediat. listy **1**:12, 1946.

The author reports on 3 patients with nevoid amentia, one of whom had the classic triad of signs: nevus flammeus on one side of the face, buphthalmos on

the same side and jacksonian fits on the opposite side. The second patient, 7 years of age, showed the typical roentgenographic sign of double lines of calcification in the occipital region. The clinical picture, pathologic changes and theories of the development of the calcifications, pathogenesis and heredity of the disease are discussed. The author tries to correlate the development of the syndrome with the age of the patient. FROM THE AUTHOR'S SUMMARY.

THE DIAGNOSIS OF CEREBROSPINAL MENINGITIS. VACLAV KREDBA, Pediat. listy **1**:71, 1946.

The diagnosis of cerebrospinal meningitis is rather difficult because the bacteriologic investigations often give normal results, particularly nowadays as the result of sulfonamide therapy. Therefore, the diagnosis has to be made on clinical grounds. The history, symptoms and signs, the course of the disease and the results of spinal fluid examinations should be carefully evaluated. In regard to the course of the disease, four clinical types can be differentiated: (1) the catarrhal, which often goes unrecognized and which can cause chronic hydrocephalus in infants; (2) the encephalitic type; (3) the drowsy type, resembling tuberculous meningitis, and (4) the fulminating type. FROM THE AUTHOR'S SUMMARY.

SUBARACHNOID HEMORRHAGE IN A TEN YEAR OLD BOY. VLADIMIR SVOZIL, Pediat. listy **1**:114, 1946.

A boy with essential or idiopathic subarachnoid hemorrhage was observed. The bleeding started as the boy bent his head while cleaning the floor. The clinical picture of subarachnoid hemorrhage is analyzed.

FROM THE AUTHOR'S SUMMARY.

TUMORS OF THE BRAIN IN CHILDREN: DIAGNOSIS AND BASIS FOR THERAPY. VON H. KRAYENBÜHL and G. WEBER, Helvet. pædiat. acta **2**:115 (April) 1947.

The exact localization and determination of the growth of a tumor by its histologic structure enables one to judge the prognosis of a brain tumor accurately. Our experience, which coincides with that of Bailey, Buchanan and Bucy and de Vet, Vincent and others, justifies our conviction that in childhood the hemispheric tumors, whether cerebral or cerebellar, often have a good therapeutic outcome with permanent cure because of the benign histologic behavior and good operative approach. But the tumors of the midline (brain stem, cerebellar vermis and ventricles) are unsatisfactorily influenced by present surgical means, on the one hand, because of their frequent malignant character (medulloblastoma, glioblastoma multiforme or pinealoma) and, on the other hand, because of the localization, i. e., the relationship to vital nervous centers (third and fourth ventricles). The hemispheric tumors, therefore, always demand good indication of the necessity for their radical removal. The majority of the midline tumors, with the exception of the craniopharyngiomas, however, must be treated by roentgenotherapy, which is frequently combined with methods of surgical decompression (drainage of ventricles and cerebellar and temporal decompression). FROM THE AUTHORS' ABSTRACT.

BLOOD-REDOX REACTION AS A TEST FOR VEGETATIVE NERVOUS FUNCTION. ARNULF MEIER and BERTA SYNEK, Helvet. pædiat. acta **2**:250 (June) 1947.

A blood reaction in vitro is described in which the reduction values of Hagedorn-Jensen show an increase by the addition of epenephrine to the blood of a healthy person and a decrease by the addition of glutathione. In the authors' opinion, this reaction is due to the redox properties of the reagents used and, therefore, it is called the blood redox reaction.

This blood redox reaction produces results differing from the normal in disturbances of the autonomic nervous system of various origins. This fact is

illustrated by examples. By means of the blood redox reaction disturbances of the autonomic nervous system may be differentiated into sympatheticotonic and vagotonic conditions.

Referring to the significance of the redox-substance in relation to the autonomic nervous system, the authors state that, compared with the result of the blood redox reaction, l-ascorbic acid (vitamin C) produces a sympathicotropic effect like epinephrine and the glutathione, in contrast, has a vagotropic effect like acetylcholine. FROM THE AUTHORS' SUMMARY.

Psychology and Psychiatry

READING AND ARITHMETIC ABILITIES ASSOCIATED WITH SPEECH DEFECTS. CHARLES E. A. MOORE, J. Speech Disorders **12**:85, 1947.

At the Proviso Township High School Speech Clinic, Maywood, Ill., 236 speech-handicapped high school students were tested by the Iowa Silent Reading Test and by the Bruecker-Van Wagenen Test. The students at the clinic averaged the same in reading ability as the school median for normal children and ranked higher in arithmetic ability. PALMER, Wichita, Kan.

DILANTIN (DIPHENYLHYDANTOIN SODIUM) TREATMENT FOR BEHAVIOR PROBLEM CHILDREN WITH ABNORMAL ELECTROENCEPHALOGRAMS. CHARLOTTE WALKER and BARBARA KIRKPATRICK, Am. J. Psychiat. **103**:484 (Jan.) 1947.

This is a report of a study on a group of outpatients from the Duke Hospital and Duke University School of Medicine, Durham, N. C. The ages of these children ranged from 7 to 12 years. All presented no abnormality on physical examinations, and none had clinical evidence of epilepsy or relatives with a history of seizures.

The children were given 30 to 100 mg. of diphenylhydantoin (dilantin®) sodium U. S. P. three times daily. The results, according to the authors, seem encouraging, though they need more follow-up work and further study. JAHR, Omaha.

THE CORNELIAN CORNER AND ITS RATIONALE. JAMES CLARK MOLONEY, in Senn, M. J. E.: Problems of Early Infancy, Transactions of the First Conference, March 3-4, 1947, New York.

Dr. Moloney describes the formation of a group dedicated to the continuance of civilization, attempting to reach its objective through research in the field of child development and family life and through education of expectant parents in the basic needs of the developing child. He and his group maintain that self-demand breast feeding and avoidance of the cultural tensions incident to infant feeding, toilet training and child discipline will result in the development of better adults. A psychologically healthy race of Americans could be produced by permissive, indulgent, supportive and consistently loving care to the preconscious child. McGUIGAN, Evanston, Ill.

ANTICIPATORY GUIDANCE OF THE PREGNANT WOMAN AND HER HUSBAND FOR THEIR ROLES AS PARENTS. MILTON J. E. SENN, in Problems of Early Infancy, Transactions of the First Conference, March 3-4, 1947, New York.

Dr. Senn describes an experiment set up at the New York Hospital in which prospective parents were given an opportunity to discuss their coming child and its care with the pediatrician who would later be in charge of the baby's welfare. The experiment appears to be successful, both parents usually showing considerable interest. Senn expresses his feeling that the experiments show that the role of the pediatrician as physician-guide to the mother could best begin before the birth of the infant. McGUIGAN, Evanston, Ill.

News and Comment

NOTICES

Transactions of Fifth International Pediatric Congress.—The "Transactions" of the Fifth International Congress of Pediatrics held in New York, July 14 to 17, 1947, are now available and can be secured from Almquist and Wiksells, Boktryckeri Aktiebolag, Huvudkontoret, Uppsala, Sweden. The price of the volume is 25 Swedish crowns.

GENERAL NEWS

Revised Edition of Booklet of Motion Picture Reviews Now Available.—The Committee on Medical Motion Pictures has completed the first revised edition of the booklet, "Reviews of Medical Motion Pictures." It now contains all the film reviews published in *The Journal of the American Medical Association* to Jan. 1, 1949. Included also is a classified table of contents, as well as a list of motion pictures obtainable through the Motion Picture Library, American Medical Association.

The reviews provide a brief description and evaluation by competent authorities of motion pictures available to the medical profession.

Copies of the booklet may be obtained on request from the Committee on Medical Motion Pictures, American Medical Association, 535 North Dearborn Street, Chicago 10.